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PORPHYRIC BULLOUS DERMATOSIS

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AND
MAX BAUM, M.D.
BALTIMORE

PORPHYRIA, a peculiar disease of metabolism in which port-wine-colored urine, containing quantities of uroporphyrin, is excreted, has been reported associated with a number of different clinical manifestations.

All normal urine of human beings contains minute quantities of coproporphyrin. Various normal values for the average twenty-four hour excretion of coproporphyrin have been given by authors using different technics, but the maximal excretion of over 100 specimens previously examined by one of us (I. Z.) represented 3 micrograms per kilogram of body weight.[1] Increased excretion of coproporphyrin, or porphyrinuria, occurs in hepatic diseases, hemopoietic abnormalities and febrile disorders.[2] On the other hand, uroporphyrin is not found in normal urine nor is it specifically found in the aforementioned pathologic states.

Porphyria is characterized by the excretion of the abnormal porphyrin, uroporphyrin, usually in such quantities that the urine is reddish brown. Many classifications of the porphyrias have been made. Günther's [3] classification has been the one usually accepted and was based principally on the course of the disease: (*a*) idiopathic acute porphyria, (*b*) toxic acute porphyria, (*c*) congenital porphyria and (*d*) chronic porphyria.

Acute porphyria, whether toxic as the result of excess drug intake or idiopathic has three clinical characteristics: (1) abdominal colic with obstipation and vomiting, (2) dark red urine containing considerable

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From the Medical Service of the South Baltimore General Hospital.

Read before the Section on Dermatology and Syphilology at the Ninety-Seventh Annual Session of the American Medical Association, Chicago, June 25, 1948.

1. Zeligman, I.: Urinary Excretion of Porphyrin in Dermatoses, Arch. Dermat. & Syph. **54**:281-291 (Sept.) 1946.

2. Vannotti, A.: Porphyrine und Porphyrinkrankheiten, Berlin, Julius Springer, 1937.

3. Günther, H.: Die Hämatoporphyrie, Deutsches Arch. f. klin. Med. **105**:89-146, 1911.

uroporphyrin during an attack and (3) degeneration of the central and peripheral nervous system, frequently followed by death.

Congenital porphyria has been described as a disorder which usually begins in childhood and in which port-wine-colored urine containing large quantities of uroporphyrin are excreted. The porphyrin is deposited especially in bone and teeth, and in about one third of the cases there is an associated hydroa aestivale with bullous lesions occurring on exposure to sunlight and recurring every spring and summer.

Chronic porphyria is a chronic condition characterized by excretion of uroporphyrin accompanied with gastrointestinal symptoms, neurologic or psychiatric abnormalities, photosensitivity or no symptoms at all. Mason, Courville and Ziskind [4] contended that chronic porphyria was frequently the asymptomatic form of acute or congenital porphyria.

Vannotti's [2] classification of the porphyrias was as follows: (1) abdominal form, (2) nervous form, (3) cutaneous form and (4) myoporphyria—cases in which there is excretion of myoporphyrin.

Brunsting and Mason [5] expressed the opinion that porphyria may be asymptomatic for years or for life. They contended that all porphyrias were congenital. Some patients might be asymptomatic, but damaging influences, such as alcohol, barbiturates and lead, could result in the clinical expressions of acute, congenital or chronic porphyria. They reasoned that it was therefore probable that some persons have the tendency toward this inborn error of metabolism and that some of these require certain damaging insults to bring out clinical manifestations.

CUTANEOUS LESIONS ASSOCIATED WITH PORPHYRIA

Of the several different dermatologic symptoms and syndromes that may occur with the porphyrias, hydroa aestivale is the commonest. It is a bullous dermatosis in which vesicles and bullae occur only on the parts exposed to solar radiation. It usually starts in childhood and in about one third of the cases is associated with congenital porphyria. The lesions appear on the face, ears, neck and dorsal surfaces of the hands and the forearms and may be followed by crusting, pyogenic infection and atrophic scarring.

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4. Mason, V. R.; Courville, C., and Ziskind, E.: The Porphyrins in Human Disease, Medicine **12**:355-439, 1933.

5. Brunsting, L. A., and Mason, H. L.: Porphyria with Cutaneous Manifestations, Proc. Staff Meet., Mayo Clin. **22**:489-494, 1947.

Though hydroa is the commonest dermatosis associated with porphyria, hyperpigmentation or melanosis, sclerodermatous changes and hypertrichosis have occurred with sufficient frequency to be noted.[6]

The acquired form of epidermolysis bullosa has also been reported in occasional association with porphyria. This condition is characterized by the formation of vesicles and bullae, followed by crusting, pyogenic infection, atrophic scarring, milia and even atrophy—as a result of trauma. Epidermolysis is not a rarity and was noted by a number of medical officers at training centers during World War II. The lesions occur on the feet, hands, knees, elbows, face and elsewhere and may be noted shortly after birth or later in life. There is some dispute whether decrease or absence of elastic tissue is responsible for this condition.

TRAUMATIC CUTANEOUS LESIONS WITH PORPHYRIA

A review of the available literature pertaining to the importance of trauma as a factor in the production of bullae in porphyric persons follows, together with the report of a clinical case.

Arzt and Hausmann[7] in 1920 described 2 siblings aged 2 and 11, respectively, with hydroa and porphyria. The one 11 years old, whose disease was noted at 5 years of age, had the typical porphyrin spectrum in his urine as well as bullae, crusts and scars on parts exposed to sunlight, particularly during the summer. There was a definite relationship to trauma in some lesions.

In 1925 Gray[8] described an 18 year old girl who was well until 5 years of age, when blisters appeared on the exposed parts of the body; these lesions recurred each summer. Blisters also appeared on the affected areas as a result of slight injuries. Her reddish urine contained porphyrin. There was also pronounced hirsutism on the face. The liver and spleen were not palpable, and the blood serum gave a positive indirect van den Bergh reaction with 2½ to 3 units of bilirubin.

Marcozzi[9] found a 10 year old patient with porphyria so sensitive to heat, light pressure and friction that bullae were produced followed by milia. Hypertrichosis was also present.

Meineri[9] described a 5 year old patient with bullae following trauma and light with sequelae of scars and milia. Hypertrichosis was evident, as was pronounced porphyria. He suggested that hydroa lesions

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6. Turner, W. J., and Obermayer, M. E.: Studies on Porphyria: II. A Case of Porphyria Accompanied with Epidermolysis Bullosa, Hypertrichosis and Melanosis, Arch. Dermat. & Syph. **37**:549-572 (April) 1938.

7. Arzt, L., and Hausmann, W.: Zur Kenntnis der Hydroa, Strahlentherapie **11**:444-459, 1920.

8. Gray, A. M. H.: Haematoporphyria Congenita with Hydroa Vacciniforme and Hirsuties, Quart. J. Med. **19**:389-392, 1926.

9. Cited by Turner and Obermayer[6] and by Borda.[18]

do not result directly from the photosensitizing action of porphyrins but that, because of the photodynamic action of these substances, the skin was altered and made more sensitive to trauma following exposure to light.

Schreus and Carrie [10] discussed the case of a 30 year old man with porphyria, whose disease started at 5 years of age. Typical blisters and scars appeared on the exposed parts, especially during the summer. Trauma was also recognized as a factor in the production of the blisters. The result of the galactose tolerance test was normal.

Gottron and Ellinger [11] reported the case of a 29 year old man whose eruption began at 7 years of age. Vesicular lesions were found on the exposed parts of the body, especially during the spring and summer. Scarring and even muscular atrophy were present. Considerable porphyrin was found in the urine, but results of tests of hepatic function were normal. Experimentally they found increased sensitivity only with the ultraviolet rays of the Kromayer lamp with pressure, and they therefore reasoned that three factors were necessary for the production of blisters: light, trauma and porphyria.

Cerutti [9] described the cases of 3 men with porphyria whose symptoms commenced in adult life. They had melanosis, hypertrichosis and bullae on the exposed parts of the body following trauma. He also reported positive Nikolsky signs in his cases. In addition, he cited a case by Radaelli in a 35 year old man with porphyria, in whom bullae appeared on exposed parts of the body following trauma.

In 1938 Turner and Obermayer,[6] in a classic article with a complete bibliography, described a case of porphyria accompanied with epidermolysis bullosa, hypertrichosis and melanosis in a 29 year old woman whose symptoms started at 20 years of age. Results of histologic study were compatible with epidermolysis bullosa. Experimental attempts to reproduce lesions by trauma and by ultraviolet irradiation were unsuccessful, but uroporphyrin I was isolated from the urine. Lesions reappeared every summer at points of trauma, especially on the hands, elbows and ankles. The liver and spleen were not palpable, and therapeutically there was no response to liver therapy.

Hübner [12] in 1940 reported a group of 7 cases in men aged 47 to 60, with pigmentation, hydroa-aestivale-like vesicles, crusts and scars on the forehead, cheeks, nose, chin and external auricles and with epi-

10. Schreus, H. T., and Carrie, C.: Beobachtungen bei einem Fall von kongenitaler Porphyrie, Dermat. Ztschr. **62**:347-357, 1931.

11. Gottron, H., and Ellinger, F.: Beitrag zur Klinik der Porphyrie, Arch. f. Dermat. u. Syph. **164**:11-43, 1931.

12. Hübner, K.: Porphyrinuntersuchungen bei einer Gruppe von Dermatosen, Arch. f. Dermat. u. Syph. **180**:289-290, 1940.

dermolysis-bullosa-like vesicles and atrophic and pigmented scars on the dorsal surfaces of the hands and fingers. In all 7 patients, evidence of hepatic damage was found by at least one test of hepatic function. The eruption was noted to be worse in spring and summer, while direct evidence of the importance of trauma was shown in 3 cases by experimental production of blisters. Porphyria was observed in all of these cases. He concluded that porphyria may be associated with hydroa vacciniforme and epidermolysis bullosa and to a greater or less extent with hepatic damage.

In 1945 Borda [13] described 6 cases in adults characterized by bullous and eroded lesions on the exposed portions of the body, hyperpigmentation and porphyria. Bullae followed by erosions and later by pigmentation were the result of exposure to sunlight, cold and trauma. Generalized pigmentation, milia, pyoderma and hypertrichosis also occurred. Reddish urine containing porphyrins was present, but uroporphyrin was not identified. His 6 cases were divided equally between the sexes, and the eruption first appeared from 29 to 58 years of age. One woman was treated with estrogenic hormones, calcium and liver extract without a favorable response.

Brunsting and Mason [5] called attention to 4 cases of chronic porphyria with cutaneous manifestations occurring in adult life. The 3 male patients and 1 female patient had bullous eruptions on the exposed portions of the body, and some had melanosis, hypertrichosis, milia and/or senile elastosis. Two had a definite family history of latent porphyria. All 4 were chronically alcoholic, and all 4 showed some liver dye retention. Trauma seemed important in at least 2 of the cases. They were unsuccessful in experimental production of the bullae.

Trauma has not been observed to play a part, however, in the production of bullae in some cases of chronic porphyria. Thus Taylor, Solomon, Weiland and Figge [14] reported a case in a 26 year old woman with bullae, crusts and scars on parts exposed to the sun and with generalized abdominal pain. The cutaneous lesions continued throughout the winter, but became worse during the summer. The urine was reddish brown and showed typical spectroscopic bands of coproporphyrin but no reddish fluorescence under Wood's light. Coproporphyrin was found (300 to 1,600 micrograms daily), but the presence of uroporphyrin was indefinite. Evidence of hepatic damage was found by the sulfobromophthalein sodium test, but results of all other tests of hepatic function were normal. Treatment with calcium lactate, sodium

13. Borda, J. M.: Porfiria ampollar y erosiva pigmentoda del adulto, Prensa méd. argent. **46**:2261-2272, 1945.

14. Taylor, I. J.; Solomon, M. L.; Weiland, G. S., and Figge, F. H. J.: Chronic Porphyria, J. A. M. A. **131**:26-29 (May 4) 1946.

bicarbonate, riboflavin, solu B® (a mixture of thiamine hydrochloride, 10 mg.; riboflavin, 10 mg.; pyridoxine hydrochloride, 5 mg.; calcium pantothenate, 50 mg., and nicotinamide, 250 mg., in powder form for injection after proper solution has been effected), crude liver extract and vitamin C were to no avail.

REPORT OF A CASE

C. H. K., 45 year old restaurateur, was first seen in dermatologic consultation by one of us (I. Z.) July 8, 1947, because of blisters and crusts on the hands, wrists, face and neck of eight months' duration.

Fig. 1.—(Weigert's stain.) Bullous lesion on the wrist. There is a large flaccid bulla containing serum and many red blood cells. The roof of the bulla is composed of slightly atrophic intact epidermis. The floor of the bulla is composed of moderately edematous collagen with a few fibroblasts and mononuclear cells. The elastic tissue fibers appear slightly broader and stain more intensely than normally, but these alterations are within the normal range for the age of the patient and for the area from which the biopsy specimen was obtained. (Description from Dr. F. A. Ellis.)

The family history was essentially normal. His second wife had active pulmonary tuberculosis and had had a thoracoplasty a year previously. There was no history of porphyria or a similar dermatosis in any relative.

His past history had been essentially normal except for a mental illness which he had had from 1941 to 1945 and from which he had apparently recovered.

His respiratory system was normal, and frequent roentgen check-ups for pulmonary tuberculosis had shown no pathologic changes. There was a mild productive cough but no hemoptysis. At times he had had spells of precordial pain, but four electrocardiograms had been normal. The patient's appetite was excellent, and there had been no recent change in weight. For years, he had been unable to tolerate fatty foods, because their ingestion caused pain in the right upper abdominal quadrant. He had noticed pinkish urine at times for the previous several months. There was no pyuria, dysuria, hematuria or renal colic. He denied venereal diseases. There was no paralysis, weakness or paresthesia. During his "nervous breakdown" several years before, he had felt persecuted and hysterical and imagined "all sorts of things," but had had no mental difficulties for the two

Fig. 2.—Arrows point to unruptured bullae on the dorsal surfaces of the fingers. There are crusted and eroded lesions as well as atrophic scarring. Amputation of three fingers of the left hand was the result of a previous injury.

years prior to examination. The patient owned a bar and was a heavy drinker. Without alcohol, he felt generally much better. He smoked 1 to 2 packs of cigarets daily and slept six to eight hours each day.

His present illness started about eight months previously, at which time blisters had appeared on the dorsal surfaces of both hands following trauma. Since then he had had recurrent bullae on the dorsal surfaces of both hands and on the forearms, neck and ears. He had noted that he was worse during the summer, following exposure to the sun. He could produce a blister on the dorsa of his hands within twelve hours after slight trauma. In fact, lesions on the forearms had never been present until the summer when he began to wear short-sleeved shirts. Many of these bullae were followed by crusts, which lasted for weeks and months. At the sites of the bullae, atrophic scarring and depigmentation resulted. He had also noted symmetric red patches on the eyelids and loss of pigment and stiffness on the cheeks and neck.

Physical examination revealed a well nourished, well developed, somewhat obese, fair-complexioned white man. There was no cyanosis, edema or jaundice. His head and neck, except for the skin, were essentially normal. The thorax was symmetric and slightly emphysematous. The chest was clear to auscultation and percussion. His heart was not enlarged to percussion, there were no murmurs, and his pulse rate was equal, normal and regular. His blood pressure was 130 systolic and 96 diastolic. His abdomen was soft, contained no palpable masses or organs and presented no rigidity or tenderness. The extremities were normal except for the skin.

His skin was fair, with considerable freckling, and his hair reddish blonde. There were a few clear half split-pea sized vesicles on the dorsa of the hands and wrists. There was a moderate number of eroded vesicles and bullae and crusted lesions on the dorsa of the hands, wrists, forearms, face, ears and back of the

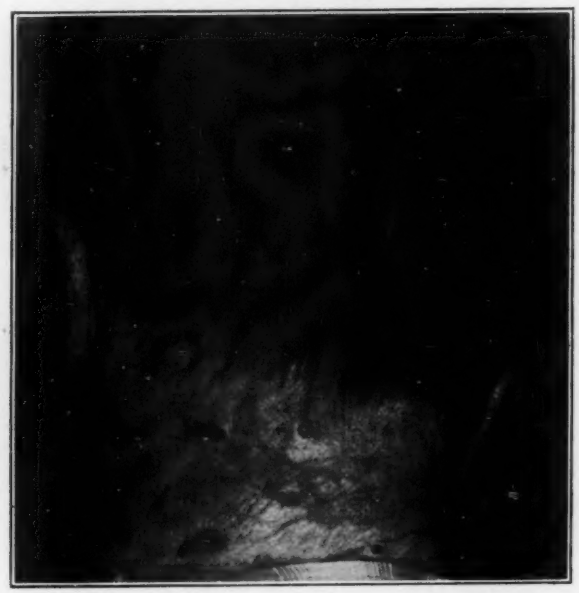

Fig. 3.—Crusted and eroded bullous lesions with sclerodermatous changes on the back of the neck.

neck and numerous areas of atrophic scarring. No lesions were present on the feet or ankles. On the cheeks and lateral and posterior cervical areas were symmetric patches of depigmentation and thickened hide-bound skin. On both upper eyelids there were reticulated telangiectasia and erythema.

The hemogram revealed 3,950,000 red blood cells, hemoglobin 85 per cent (14.5 Gm.) and 6,900 white blood cells. The result of the serologic test for syphilis was negative. A routine urinalysis revealed no albumin or sugar, but the urine was pinkish in ordinary light and revealed red fluorescence with Wood's light. The urine was examined on a number of occasions, and each examination revealed red fluorescence with Wood's light, whereas all control specimens were yellowish, green or light blue with Wood's light.

He was treated with crude liver extract, 1 cc. intramuscularly, for eight weeks without improvement. He was given various topical medications, such as penicillin ointment for the pyococcic aspect of the crusted lesions, antipruritic ointments,

sun-filtering ointments containing cycloform® (isobutyl paramiobenzoate), and a chlorophyll-containing ointment for the promotion of epithelization—none of which was spectacularly effective. Avoidance of alcohol made him feel much better generally, but did not influence the occurrence of lesions. Treatment with tripelennamine hydrochloride was tried, but could not be tolerated because of nausea and vomiting. He had, of course, been directed to avoid exposure to the sun and trauma.

Tests with ultraviolet rays revealed no remarkable sensitivity. The biopsy showed a subepidermal bulla, with apparent complete separation of epidermis from the dermis and with both epidermis and dermis intact. Weigert's stain showed alteration of elastic fibers consistent with the age of the patient and the area from which the biopsy specimen was taken. A study of several twenty-four hour specimens of urine revealed an average of 248 micrograms of coproporphyrin, which is within normal levels for his weight (2.2 micrograms per kilogram). Considerable uroporphyrin was present in the urine; the presence of this abnormal porphyrin established the diagnosis of porphyria. Insufficient cooperation from the patient prevented the pooling of enough urine to obtain adequate amounts of uroporphyrin for isolation. The extraction of both porphyrins and the quantitative measurement of coproporphyrin were performed as described in a previous report.[1] (Dr. E. H. Maechling, of the Department of Dermatology, Columbia College of Physicians and Surgeons, made the quantitative determination of the coproporphyrin, as adequate facilities for such were unavailable to us at that time.) The uroporphyrin bands in 12 per cent ammonium hydroxide were: 6,600 to 6,550 angstrom units and 6,200 to 5,940 angstrom units.

On September 10 he was admitted to the South Baltimore General Hospital to the private service of one of us (M. B.) for study. History and physical examination revealed nothing which had not previously been noted and recorded, but further laboratory studies especially directed at hepatic function were emphasized.

The urine was amber, with a specific gravity of 1.017. The results of tests for albumin were negative, for glucose negative and for urobilinogen positive. A complete blood cell count showed 96 per cent hemoglobin, 4,700,000 red blood cells and 8,100 white blood cells, with a differential count of 61 per cent polyphonuclear neutrophils, 36 per cent monocytes and 3 per cent band forms. The result of the Kahn test of the blood was negative; the blood sugar was 140 mg. per hundred cubic centimeters (two days later 100 mg.) and the blood nonprotein nitrogen was 40 mg. per hundred cubic centimeters. A series of tests of the gallbladder revealed a poor shadow of the gallbladder, with no evidence of stones. The prothrombin time was eighteen seconds (normal sixteen seconds). The results of the cephalin flocculation test were negative in twenty-four hours and 1 plus in forty-eight hours. The sulfobromophthalein sodium test revealed 36 per cent retained after fifteen minutes and only a trace after thirty minutes. Blood cholesterol was 195 mg. per hundred cubic centimeters. Total serum protein was 6 mg. per hundred cubic centimeters, with albumin 3.3 mg., globulin 2.7 mg. and an albumin-globulin ratio of 1.2. The results of the van den Bergh test was negative. The icteric index was 1 acetone unit.

By late October he began to improve, but he still had some new vesicles following trauma. By December 10 there were no further active lesions. Later during the winter, he had no active bullae but complained mainly of the stiffness of the neck and cheeks associated with the sclerodermatous changes. The urine at this time was still pinkish and still showed red fluorescence.

COMMENT

No attempt is being made in this paper to discuss the chemical, physiologic or metabolic aspects of the porphyrins. For these, the reader is referred to several excellent monographs on the subject.[15] Suffice it to say that coproporphyrin is normally excreted in the urine in minute quantities. Increased excretion of urinary coproporphyrin, called porphyrinuria, occurs with febrile diseases, hepatic disorders and hemopoietic abnormalities,[2] while a previous study by one of us [1] failed to show any significant increase in urinary excretion of coproporphyrin in many dermatoses, including those believed to be caused or exacerbated by light. The only dermatosis which was associated consistently with porphyrinuria was acute disseminate lupus erythematosus, but this is easily explained by the accompanying hyperpyrexia. No uroporphyrin was observed in that series.

The patient described in this paper was referred to us because of blisters at sites of trauma. The history and the lesions themselves were consistent with acquired epidermolysis bullosa, but because the feet were not involved, because the lesions were present on the exposed portions of the body only and because there was an exacerbation during the summer, with an extension of the lesions up the forearms associated with the wearing of short-sleeved shirts, the possibility of porphyria was considered. When questioned about the color of his urine, the patient replied that his wife had called his attention to a pinkish red discoloration a few months previously. A spot specimen of urine was thereupon examined and definitely was pinkish. When visualized with Wood's light, there was very evident reddish fluorescence. On his next visit he brought a twenty-four hour specimen which also had the pinkness and the red fluorescence, a persistent observation in all subsequent examinations. The urinary excretion of coproporphyrin was within normal limits, but the abnormal uroporphyrin was present. Unfortunately, no standards were available for an estimation of its excretion in a twenty-four hour specimen. The presence of uroporphyrin, however, definitely established this as a case of porphyria, since uroporphyrin is not found in normal urine.

The most frequent dermatosis accompanying porphyria is hydroa aestivale, characterized by vesicles and bullae followed by crusting and atrophic scarring on those parts of the skin exposed to solar radiation. This condition commonly starts in childhood, and in some cases trauma has been noted as a factor in the production of the lesions.

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15. Vannotti.[2] Mason, Courville and Ziskind.[4] Dobriner, K., and Rhoads, C. P.: The Porphyrins in Health and Disease, Physiol. Rev. **20**:416-468, 1940.

Hyperpigmentation and hypertrichosis have been not infrequently noted in conjunction with porphyria, but these were not present in this instance. On the other hand, scleroderma, which may occur as a sequel in some cases, was present on the face and especially the neck. In fact, during the winter months the patient's chief complaint was stiffness of the neck.

Epidermolysis bullosa has been noted with some cases of porphyria and was considered as a possibility in this instance. A study of reported cases and our own reveals, however, that when porphyria is a factor in trauma-produced bullae, the lesions occur only on those parts of the skin exposed to sunlight. Our patient traumatized his skin lightly for us on exposed and nonexposed parts, with the subsequent formation, twelve hours later, of bullae only on the parts exposed to sunlight. Furthermore, his condition was exacerbated during the summer and the eruption receded during the winter. Therefore, we concluded that three factors were necessary for the production of this syndrome: porphyria, sunlight and trauma. We believe that in all cases of suspected epidermolysis bullosa, especially of the acquired type which is limited to the exposed portions of the body, the possibility of porphyria must be considered. We do not believe, however, that all cases of hydroa or epidermolysis occur in association with porphyria.

Many authors have considered hepatic damage as an important factor in the porphyrias, and some have found evidence for this hypothesis. Our patient was hospitalized with this in mind and despite various tests, hepatic function was found to be within normal limits. If hepatic damage is present, possibly the liver reserve of our patient was such that none of the tests revealed dysfunction.

We are inclined to agree with Brunsting and Mason [5] that some persons congenitally have the tendency to this inborn error of metabolism and that some require certain damaging insults to bring out clinical symptoms. As in their cases, our patient also was chronically alcoholic and alcohol undoubtedly played a major precipitating role. Others have reported barbiturates, lead and other chemicals as precipitating factors.

Chronic porphyria, as exemplified by our case, may be associated with neuropsychiatric and gastrointestinal symptoms as well as cutaneous ones. Whether the psychosis which had required the patient's institutionalization was associated with the porphyria is difficult to evaluate in view of the failure of any one at that time to take notice of the coloration of his urine. A similar indecisive conclusion must be taken of his gallbladder colicky complaints similar to those reported in acute and chronic porphyria.

In most cases of porphyria and/or hydroa aestivale there is no increased erythematous sensitivity to light nor can one usually experi-

mentally produce lesions with sunlight or selected wavelengths of ultraviolet rays. Our case was no exception in this respect, at least insofar as sensitivity to mercury vapor ultraviolet rays was concerned. A carbon arc source of ultraviolet rays would be more appropriate for cases of porphyria, but such a source was unavailable to us.

Meineri [9] was the first to suggest that hydroa lesions do not result directly from the photosensitizing action of porphyrins but that, because of the photodynamic action of these substances, the skin is altered and made more sensitive to trauma after exposure to light. Gottron and Ellinger,[11] in a case of porphyria, experimentally found increased sensitivity only to the ultraviolet rays of the Kromayer lamp with pressure, and they therefore reasoned that three factors were necessary for the production of the blisters: light, trauma and porphyria. Hübner,[12] in 7 cases of porphyria with blisters on exposed portions of the body, was able experimentally to produce blisters traumatically in 3 cases. Blum and Pace,[16] in discussing the failure of experimental photosensitization to porphyrins, hypothesized that hydroa lesions result from trauma rather than from light.

As a result of a review of the literature and observations in our case, we also believe that the blisters present in porphyrias, whether they have hitherto been called hydroa aestivale or epidermolysis bullosa, are all essentially the same and are the result of some change in the skin due to the presence of the photodynamic uroporphyrin which makes it more susceptible to a combination of light and trauma. Thus porphyria, sunlight and trauma are all necessary factors in the production of the bullae. It is therefore our opinion that "porphyric bullous dermatosis" is the best inclusive term for this condition, since the porphyria is the essential biochemical basis for this clinical entity.

SUMMARY

The bullous eruptions that occur with porphyrias are reviewed with special emphasis on the factor of trauma. A case is reported in a chronically alcoholic patient with chronic porphyria in whom trauma was a factor in producing bullae on the skin exposed to sunlight.

As a result of a review of the literature and our own case study, we believe that the bullous eruptions present in porphyric patients, whether hitherto named hydroa aestivale or epidermolysis bullosa, are essentially the same and are the result of some change in the skin due to the presence of the photodynamic uroporphyrin which makes it more susceptible to light and/or trauma. By no means, however, are all cases

16. Blum, H. F., and Pace, N.: Studies of Photosensitization by Porphyrins. Brit. J. Dermat. **49**:465-487, 1937.

of hydroa or epidermolysis of porphyric causation. We propose the use of the term "porphyric bullous dermatosis" for the disease in such cases.

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ABSTRACT OF DISCUSSION

DR. LOUIS A. BRUNSTING, Rochester, Minn.: This is an excellent presentation of a difficult subject. The distinctive feature of porphyria is that abnormal kinds and amounts of porphyrins, especially uroporphyrin, are excreted in the urine and feces, but there is some argument as to whether the particular isomer of porphyrin that is excreted is exactly the basis for definition of the classification of the type of porphyria that is present. Porphyria is a rare familial metabolic fault with various forms of clinical expression; persons with the disease may be asymptomatic for years or for life, and often the urine does not have a port wine color even when it contains abnormal porphyrins. Surveys of families in which this inborn error of metabolism occurs may disclose the presence of uroporphyrin or the colorless porphobilinogen in the urine of apparently normal persons. Tests for porphyrins, at least qualitative tests, are not beyond the range of most hospital facilities, for no elaborate equipment is required.

In acute porphyria, pigmentation occurs, and sometimes solar urticaria, but other cutaneous reactions are infrequent; in congenital porphyria, the outstanding change is the hydroa-like reaction of the light-exposed surfaces of the skin as well as erythrodontia. Bullous eruptions occur in the adult with chronic porphyria (often as the presenting symptom), as in the case under discussion, which I like to consider an example of the tardive form of congenital porphyria. Such cases are probably commoner than is generally supposed. Under the influence of light and of minor trauma, lesions similar to those seen in epidermolysis bullosa develop in the exposed skin. The latter condition represents a hereditary fault in the binding mechanism of the skin, but no actual relationship between true epidermolysis bullosa and porphyria has been established. Other changes which occur regionally in the skin in chronic porphyria are pigmentation, hirsutism, milia and an alteration in texture which resembles scleroderma. Microscopically, such skin shows the picture of senile elastosis, particularly in regard to the peculiar staining reaction of the collagen.

Little is known concerning the factors which may precipitate the manifest syndrome of porphyria or which may influence its course one way or another. In certain cases, a damaging influence on the liver, either by disease, such as cirrhosis, or by hepatotoxic drugs or poisons (alcohol, barbiturates, arsenic, lead) appears to contribute to the development of obvious symptoms of porphyria. Within a comparatively short period of time, I have observed 5 patients with chronic porphyric bullous dermatosis as described herein; in each instance a history of chronic alcoholism and evidence of hepatic dysfunction were present, and it seemed reasonable to relate these factors to the precipitation of the clinical syndrome. It has been claimed that three factors are necessary for the production of blisters: light, trauma and porphyria. However, this does not explain the absence of symptoms in cases of latent porphyria even when there are large amounts of uroporphyrin in the urine. I would offer an added factor for consideration, that is, damage to the liver, perhaps of a degree unmeasurable by current tests of hepatic function. The exact mechanism is unknown. Perhaps the damaged liver influences the

enzyme system of the skin, which, in the presence of porphyria, affects the binding qualities of the connective tissue in the regions that are exposed to light. In my experience, the general health of these patients improves and the cutaneous symptoms subside under an anticirrhotic regimen.

DR. GEORGE H. CURTIS, Cleveland: I had the opportunity to observe briefly a case which I consider similar to that of Drs. Zeligman and Baum. The patient was a white laborer aged 49, whom I saw in July 1947. The disease had its onset in May 1946, and in the early stages he found it practical to keep his sleeves down to prevent lesions on the forearms. The face, neck, ears and hands were sites of itching papules and blisters, which were more numerous and severe in summer. In the winter the face and neck were free of lesions, but bullae continued on the hands. The family history and general physical examination elicited no unusual observations. The face, neck and hands were deeply tanned, and the skin of the neck was considerably weatherbeaten. There was also lichenification. Excoriations, several small denuded lesions and urticaria-like maculopapules were present. A single pea-sized bleb was located on the nape of the neck. Bullae, scars and milium-like lesions in old atrophic scars were evident on the fingers and knuckles.

The results of the routine hemogram, urinalysis and blood sugar test were within normal limits. The observations of histologic examination of a bulla excised from the hands were considered consistent with those of epidermolysis bullosa. On two successive days the urine was qualitatively examined for porphyrins, with positive results; unfortunately, the porphyrins were not identified. Attempts to produce lesions with the Kromayer lamp and by compression with a quartz filter were unsuccessful. Six hours after pinching the dorsum of the left hand a bulla appeared at the site. However, no bullae appeared on the forearms or neck where tested. In October 1947 the patient exhibited improvement of the face and neck, but bullae remained on the hands. A twenty-four hour urine specimen at this time showed no porphyrins. The patient has since been inaccessible for observation. The number of cases of this syndrome seems to be increasing. After studying the literature, I believe that identification depends on the establishment of routine laboratory procedures for at least the qualitative identification of porphyrins.

Clinical observation leaves no doubt that certain dermatoses are produced by the photosensitizing effect of sunlight as exemplified by urticaria solare and hydroaestivale without porphyrinuria. The role of porphyrins in photosensitivity of the skin is equivocal. Hematoporphyrin and some of the naturally occurring porphyrins are known to induce photosensitivity. The porphyrins are deposited in the tissues and have been found high in the papillae of the dermis. Thus the conditions sunlight, porphyrinuria and fixation of porphyrius in tissue are simultaneously present for the development of photosensitivity and the production of the lesions of hydroa aestivale and the epidermolysis-bullosa-like dermatoses. On the whole, however, experimental attempts to reproduce the lesions by artificial light, as well as controlled sunlight, have not been successful. Blum and Pace (Studies of Photosensitization by Porphyrins, *Brit. J. Dermat.* **49**:465-485 [Nov.] 1937) observed vesiculation at the sites of subepidermal injection of hematoporphyrin in a normal subject following exposure to sunlight nine weeks later. However, hematoporphyrin does not occur as such in disease in human beings.

It is also difficult to evaluate trauma in the production of lesions in the porphyrin-sunlight-trauma complex. In the case of Drs. Zeligman and Baum, and in mine, bullae were produced by slight trauma only on the exposed skin. In Meineri's case, cited by the authors, bullae appeared only after trauma, even

though the patient's skin was deeply pigmented on prolonged exposure to sunlight. Nevertheless, bullae may be produced by pressure with a Kromayer lamp and quartz filter in a normal person. Bullae have been reported to occur only on the feet, the quantity more numerous in summer, in a case of porphyrinuria with epidermolysis bullosa. Trauma is followed by bullae in the absence of sunlight and porphyrinuria in epidermolysis bullosa.

During the summer months there is a certain amount of swelling and edema of the dependent parts of both upper and lower extremities and traumatic blistering occurs more readily than in cooler seasons. Among other factors I believe that the borderline normopathologic state of the vascular bed in the dermis plays some part in the increase of symptoms in epidermolysis bullosa with or without porphyrinuria. One wonders whether the porphyrins are as important as genetics, sunlight, trauma and other factors in the production of lesions in hydroa aestivale and epidermolysis bullosa.

Dr. Israel Zeligman, Baltimore: Our purpose in presenting this paper was twofold: We wished to stimulate and restimulate interest in the porphyrins and the porphyrias in their relationship to the dermatoses; secondly, we wished to call attention to the possible importance of porphyria in the acquired and possibly in the congenital types of epidermolysis bullosa. We think that every case of epidermolysis bullosa should be studied in this direction.

EOSINOPHILIC GRANULOMA

With Simultaneous Involvement of Skin and Bones

JAMES H. McCREARY, M.D.
COLUMBUS, OHIO

EOSINOPHILIC granuloma of the bone has been established as a disease entity by Otani and Ehrlich [1] and by Lichtenstein and Jaffe,[2] in 1940. The eosinophilic granulomas of the skin as reported in the literature have recently been reviewed by Weidman,[3] Lewis and Cormia,[4] Lever [5] and Dobes and Weidman.[6] The cutaneous manifestations of eosinophilic granuloma have varied so widely in their clinical and histopathologic features that the disease is not yet considered as a disease entity.

REPORT OF A CASE

V. M.,[7] an 11 year old white girl, was first seen at the University of Chicago Clinics on Jan. 9, 1947. She complained of tender tumefactions and ulcerations of the skin on the upper part of the chest and scalp. She had been well until the age of 2 years, when she became ill with measles and mumps at the same time. During this illness adenitis of the right submaxillary gland developed, which failed to resolve, and then an ulcer formed. Abscesses of nearby nodes developed and followed a similar course. Since that time the patient has been almost continuously sick, with swelling and ulceration of lymph nodes on the head, neck and thorax. The appearance of each new lesion has been accompanied with a temperature of

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From the Section of Dermatology, University of Chicago (Chief of Service, Dr. Stephen Rothman).

1. Otani, S., and Ehrlich, J. C.: Solitary Granuloma of Bone Simulating Primary Neoplasm, Am. J. Path. **16**:479, 1940.

2. Lichtenstein, L., and Jaffe, H. L.: Eosinophilic Granuloma of Bone, with Report of a Case, Am. J. Path. **16**:595, 1940.

3. Weidman, F. D.: The "Eosinophilic Granulomas" of the Skin, Arch. Dermat. & Syph. **55**:155 (Feb.) 1947.

4. Lewis, G. M., and Cormia, F. E.: Eosinophilic Granuloma, Arch. Dermat. & Syph. **55**:176 (Feb.) 1947.

5. Lever, W. F.: Eosinophilic Granuloma of the Skin, Arch. Dermat. & Syph. **55**:194 (Feb.) 1947.

6. Dobes, W. L., and Weidman, F. D.: Granulomatous Hodgkin's Disease of the Skin with Extreme Eosinophilia, Arch. Dermat. & Syph. **55**:212 (Feb.) 1947.

7. The patient was presented before the Chicago Dermatological Society on Feb. 19, 1947. At that time studies of the case were incomplete. The presentation of this case has been made possible through Dr. Mila Pierce of the Pediatric Department of the University of Chicago Clinics who has been responsible for the medical care of the patient.

99 to 104 F. and locally by pain, tenderness and erythema. After rupture of the abscess, the systemic symptoms disappeared. There was a tendency toward slow healing with granulation and scar formation. Following an operation three years previously, in 1944, for the removal of a group of cervical glands, the motion of the shoulders and neck has been restricted because of pain. Roentgen therapy seemed to accelerate healing, with remissions of the symptoms for as long as a year. The total roentgen dosage given to each lesion varied with the depth and extent of the lesion and was between 90 and 660 r. Penicillin and the sulfonamide drugs had no effect on the course of the disease. The disease had been diagnosed at one time as tuberculosis by smear examination and at another time as Hodgkin's disease by lymph node examination.

On examination, the patient appeared to be slightly undernourished. She was afebrile and not acutely ill. Both shoulders were carried forward and elevated.

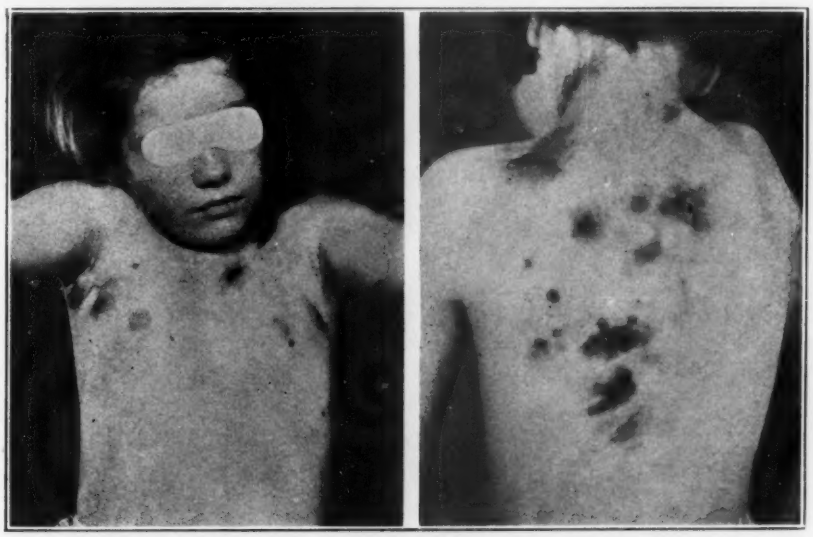

Fig. 1.—*A,* clinical photograph of eosinophilic granuloma, showing the unruptured abscesses in the right axilla and some irregular ulcerations of the left upper part of the thorax. *B,* irregular deep ulceration and scarring of eosinophilic granulomas of the neck and back. The abscesses appeared in regions where large lymph nodes are not usually seen.

There was moderate scoliosis toward the right, with moderate reduction of movement to the left hemithorax. A firm spleen was palpable. The liver was felt at the costal margin. The enlarged cervical nodes showed a tendency to mat together. The ulcers of the overlying skin were from 2 to 5 cm. in diameter and had soft undermining irregularly shaped edges and irregular granulating bases well vascularized. Some of the ulcers appeared in regions where large lymph nodes are not usually present. The results of the rest of the physical examination were essentially normal (fig. 1).

The roentgenogram of the skull revealed an irregular oval dehiscence about 2 cm. in diameter, in the right parietal bone under one of the tender swellings. All other bones were normal, including the ribs under the cutaneous ulcerations (fig. 2).

Culture of the exudate on blood agar and Sabouraud's mediums showed Staphylococcus albus. Acid-fast stains were repeatedly negative. Blood culture and repeated animal inoculations into rats and guinea pigs were negative. Reactions to a tuberculin patch test and blastomycin, histoplasmin and purified protein derivative tests were all negative. Reactions to Kahn tests were negative. A sternal puncture showed the myeloid-erythroblast ratio to be elevated. The sedimentation rate varied between 6 and 41 mm. The white blood cell counts were 8,000 to 25,000; hemoglobin was 11.5 to 14.5 Gm.; the red blood cell counts were 3,800,000 to 5,200,000. The differential count revealed: polymorphonuclear cells

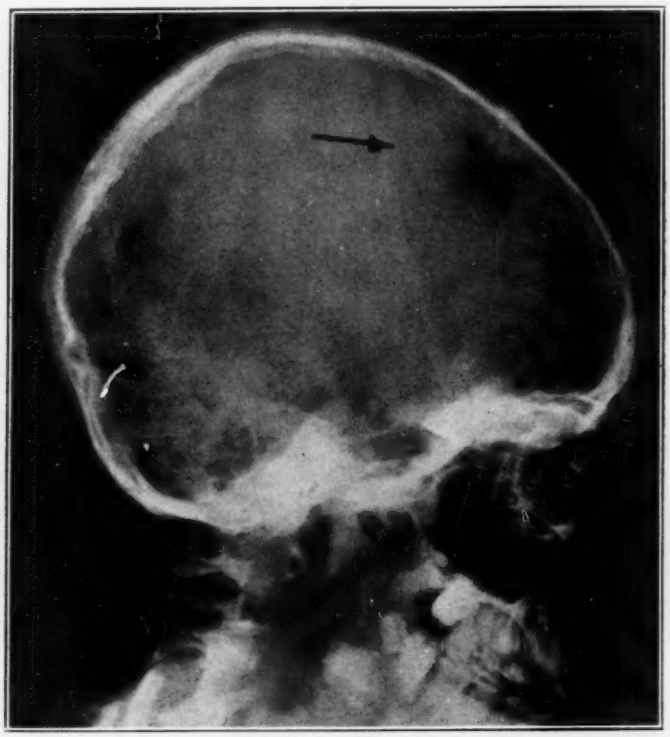

Fig. 2.—Roentgenologic examination of the skull, demonstrating an irregular dehiscence of eosinophilic granuloma in the right parietal bone (arrow). The rest of the skeleton showed no evident abnormality.

72 per cent, lymphocytes 26 per cent and eosinophils 2 per cent. Hematocrit was 41. The urine was normal. Serum lipids were normal

An axillary lymph node removed on January 30 was a large moderately firm node, red-brown and mottled with small lighter (tan) areas. The microscopic sections showed an extensive obliteration of the normal architecture, although small remnants of cortical follicles and cords filled with lymphocytes remained. Sheets of large acidophilic or pale nonfoamy macrophages seemed to have filled in the sinuses as well as the parenchyma. Scattered in great abundance between them were eosinophils and lymphocytes. Some cells with dark nuclei looked like normoblasts. The histiocytes or macrophages frequently had lobulated nuclei, and some

were multinucleated. Neither in their cytoplasm nor in their nuclear form did they resemble Reed-Sternberg cells. There was fibrous thickening of the capsule and decided fibrosis of some of the cell-filled lymphatic sinuses. Fibrous tissue was especially dense around the blood vessels of the hilar portion of the node. Evident in Mallory stain was the presence of clefts or small vacuoles of the cytoplasm of the large macrophages. However, the appearance was different from that seen in the large cells of Gaucher's disease, Niemann-Pick or Hand-Schüller-Christian xanthomatoses. Stains for gram-positive and acid-fast bacteria were negative. Sudan stain revealed an occasional macrophage containing lipid and, in addition, a small amount of lipid material in the fibrous septums. A small amount of this lipid was anisotropic (fig. 3 and 4).

Fig. 3.—Eosinophilic granuloma. Section from an axillary lymph node (hematoxylin and eosin × 11), showing the extensive obliteration of the normal architecture of the node.

Histologic section of granulation tissue from a sinus revealed many eosinophils, large mononuclear cells with acidophilic protoplasms and lipid content, a few lymphocytes and necrotic debris (fig. 5).

The lesion of the right parietal bone was curetted out completely and found to be located immediately beneath the galea and extending down to the inner table, which was intact. The lesion consisted of a mass of brownish granulation tissue. The outer table of bone was padded and eroded. Microscopic study of the granulating mass showed large acidophilic and nonfoamy macrophages with large irregular-shaped nuclei, indistinct nucleoli and moderate amount of cytoplasm. Many of these macrophages were binucleated, and there was some infolding of the nuclear membrane. Scattered among these cells were a moderate number of eosinophils and a few lymphocytes. There were a few multinucleated giant cells, some of these containing vacuoles or slitlike spaces. A stain for fat (sudan IV)

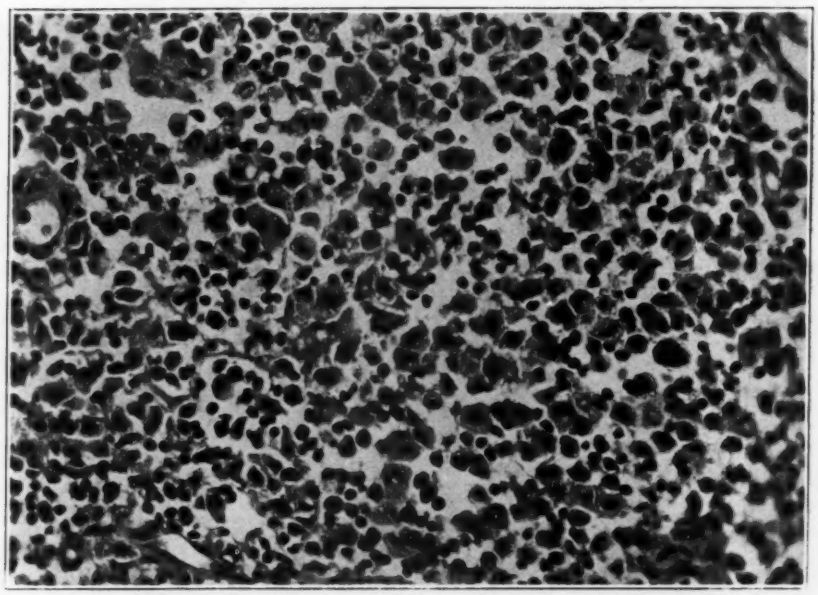

Fig. 4.—Section of axillary node at higher magnification (hematoxylin and eosin × 480), demonstrating large macrophages or histiocytes. Many of the macrophages are multinucleated. Eosinophils and lymphocytes are scattered among the histiocytes.

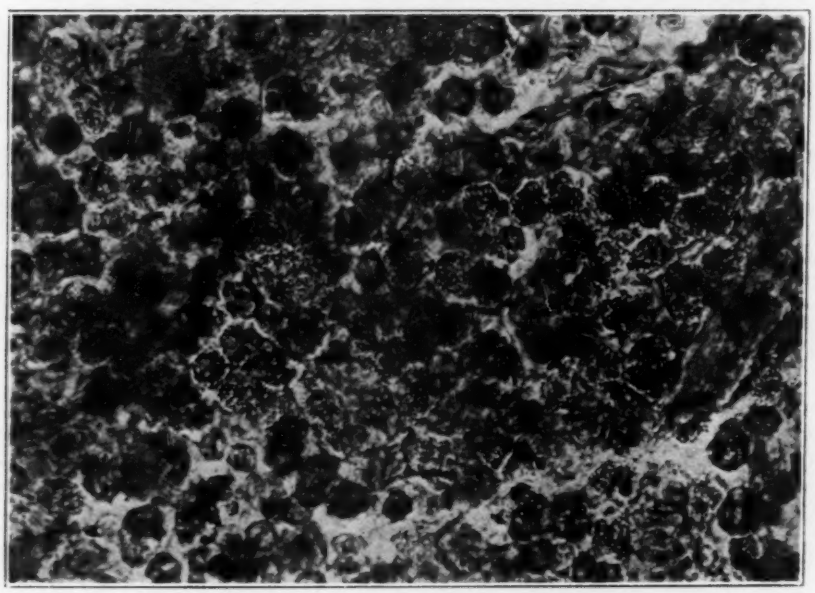

Fig. 5.—Eosinophilic granuloma. Section from the lesion in the right parietal bone (sudan IV stain × 950), showing the lipoprotein granules in the numerous macrophages. Most of the lipoprotein granules were not anisotropic.

revealed that a moderate number of the macrophages contained fat droplets, or lipoprotein granules, most of which were not anisotropic.

Study of the microscopic sections of the cutaneous lesions showed a thinned out epidermis with a shortening of the rete pegs on the border of the ulcer. There was a decided inflammatory infiltrate in the dermis consisting of macrophages, plasma cells, lymphocytes, eosinophils and polymorphonuclear neutrophils. Beneath the dermis there were sheets of reticulum-like cells with a moderate amount of faintly acidophilic cytoplasm, blurred cell outlines, large and pale nuclei and a faint chromatin network. The nuclei were irregularly shaped, and many of them were indented. Inflammatory cells were scattered among the sheets of reticulum cells, and a few foreign body giant cells were seen. In some of the pieces there were many capillaries (fig. 6).

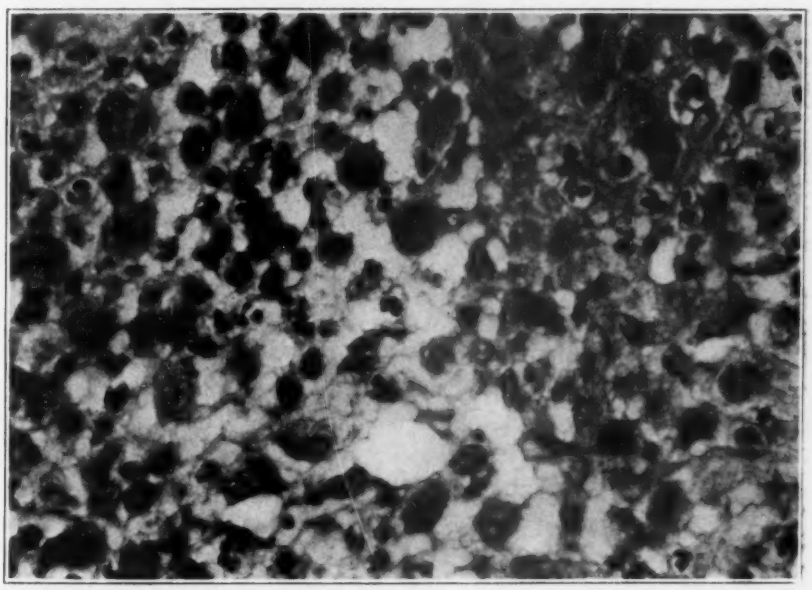

Fig. 6.—Eosinophilic granuloma. Section from an abscess in the skin (hematoxylin and eosin × 950), showing the pronounced inflammatory infiltrate consisting of macrophages, lymphocytes, eosinophils and polymorphonuclear neutrophils.

The response of the cutaneous lesions to high voltage roentgen therapy was favorable. Each lesion received at least 500 r, and some received as much as 1800 r in fractionated doses (130 kilovolts, 50 cm. focus-skin distance, 20 milliamperes, 0 filter and 0.25 half-value layer). After each course of roentgen therapy, the lesions were improved considerably or healed entirely. However, new ones would develop during the course of roentgen therapy. Injections of radioactive phosphorus (P-32) were started later. A total of 2,200 microcuries were given intravenously in two courses, with a daily dosage of 200 to 300 microcuries. For a few days during the last course, the lesions seemed to be aggravated. They drained considerably, and new lesions developed. The temperature increased temporarily to 40.2 C. (104.4 F.). Beta hemolytic streptococci were cultured from the draining sinuses on several occasions during this episode. The patient was given sulfadiazine by mouth, penicillin parenterally and an aluminum oxide paste locally.

After this setback, the patient improved rapidly and was discharged Jan. 8, 1948. The granulomas showed healing with granulation and scarring. The therapy in the hospital included ultraviolet irradiation to the whole body, supplementary vitamins and physical therapy to the shoulder girdle. It is too early to determine what effect the radioactive phosphorus may have had on the course of the disease.

COMMENT

This is the second case reported in which cutaneous manifestations accompanied a granuloma in the bone. The first case of this kind, with simultaneous but independent involvement of skin and bone, was reported by Curtis and Cawley [8] in June 1947.

The disease in my case had been diagnosed previously as cutaneous tuberculosis from a smear; yet in this department all animal inoculations, smears and reactions to tuberculin tests were negative. The results of examination of microscopic sections did not favor a diagnosis of tuberculosis, and it is difficult to imagine that the eosinophilic reaction could be masking an underlying tuberculous process. A few giant cells were present, but these were identified as foreign body type. The chest was clear, and no other tuberculous focus could be found.

The disease had also been diagnosed at one time as Hodgkin's disease. The sections of the present review certainly do not show Sternberg-Reed cells or other characteristic features of Hodgkin's disease. It has been emphasized by Weidman [3] that "an inter-current eosinophilous disease or at least pathologic substrate can modify or obscure an otherwise readily diagnosable entity," and a masking of Hodgkin's disease should be perhaps considered in this case. The clinical course, however, with the onset in a 2 year old girl and slow progression over a twelve year period, does not suggest Hodgkin's disease at all.

Because of the presence of lipid deposited in moderate amount in macrophages of the sinus tract and of the granuloma of the bone, this condition may be allied with the lipoidoses. Some of the lipid granules were anisotropic, but the majority were not. Foam cells, typical of the xanthomas, were not frequently seen.

Microscopically, the picture resembled most closely the picture seen in the eosinophilic granuloma of bone as described by Lichtenstein and Jaffe [2]: soft brownish granulation tissue which presented on microscopic section sheetlike collections of large phagocytic cells of the nature of histiocytes, with a moderate amount of cytoplasm, many of them binucleated; presence of a moderate number of eosinophils, and multinucleated giant cells which contained vacuoles or slitlike spaces and, in some instances, sudanophilic droplets. In the case reported, not

8. Curtis, A. C., and Cawley, E. P.: Eosinophilic Granuloma of the Bone with Cutaneous Manifestations, Arch. Dermat. & Syph. **55**:810 (June) 1947.

only did the bone lesion present this picture but also the same eosinophilic granulomatous process was evident in the lesions of the skin. The appearance of the macrophages was different from that seen in the large cells of Gaucher's, Niemann-Pick or Hand-Schüller-Christian disease.

Clinically, my patient had a protracted course. She had never been critically ill. Letterer-Siwe disease makes its appearance mainly in infants and in children below the age of 2 and usually runs an acute or subacute course fatal within a matter of weeks or months.[2] The soft tissues as the lymph nodes, the tonsils, the thymus, the spleen, the bone marrow, the liver, the lymphoid tissue of the alimentary tract and the skin may show histiocytosis in Letterer-Siwe disease. Only the lymph nodes in this case showed significant enlargement. Although the disease was noted shortly after both measles and mumps, the patient's temperature remained normal except for elevations when new lesions first appeared. Purpura and eczematoid dermatitis, rather characteristic for Letterer-Siwe disease, were absent in this case. The abscessed lymph nodes showed considerable eosinophilia, which ordinarily is not found in Letterer-Siwe disease. The peripheral blood did show mild hypochromic anemia at times, whereas such anemia is steadily progressive in Letterer-Siwe disease.

As of the time of reporting, neither diabetes insipidus nor exophthalmos had developed in the patient. Examination showed that the involvement of the skull bones had not been extensive enough to include the sphenoid and the bones delimiting the orbit. Classic Hand-Schüller-Christian disease certainly can be excluded on the basis that diabetes insipidus and exophthalmos had not developed, and thus the triad of exophthalmos, diabetes insipidus and calvarial defect was far from being complete.

Isolated eosinophilic granuloma of the skin with no involvement of bones and internal organs was reported by several authors. Lewis and Cormia,[4] Lever [5] and Buley [9] have extensively reviewed the American and European literature describing these cases. The clinical appearance of these lesions has greatly differed from those reported by Curtis and by me, insofar as the isolated cutaneous lesions have been described heretofore as benign indolent nonulcerating nodules or plaques, red or purplish, sometimes with a yellowish tinge, sharply marginated and located about the head or over the joints. In addition, the isolated benign cutaneous lesions have not been accompanied with lymphadenopathy, and some of them have proved to be radioresistant.

9. Buley, H. M.: Eosinophil Granuloma of Skin, J. Invest. Dermat. **7**:291 (Dec.) 1946.

Although miscroscopically the features of cutaneous "benign" eosinophilic granulomas are comparable to that of my case, in the latter there was more phagocytic activity than in the cases reported in the other group. The analysis leads to the conclusions that benign nonprogressive eosinophilic granuloma of the skin is an entity different from the condition in the case reported by Curtis and by me.

SUMMARY

A case with calvarial bone defect and with cutaneous ulcerations is reviewed. The cutaneous ulcers originated partly in the skin proper, and developed partly over abscessed lymph nodes with draining sinuses. Histologically, eosinophils and histiocytic macrophages were the prominent features. Unusual features of this case are: onset in a 2 year old girl, protracted course over eleven years, simultaneous presence of cutaneous and bony lesions in different regions, lymphadenopathy and radiosensitivity of the lesions. The differential diagnosis of Hodgkin's disease, eosinophilic granuloma of the bone, eosinophilic granuloma of the skin, Letterer-Siwe disease and Hand-Schüller-Christian disease is discussed.

The lesions in the case reported showed remarkably good response to bone curettage, local roentgen irradiation and intravenous radioactive phosphorus (P-32) therapy.

The case reported closely resembles that of Curtis. The histologic features in both these cases were similar to those of benign isolated eosinophilic granuloma of the skin. However, they definitely differed from the features in cases of benign disease, representing systemic disease with bone and soft tissue destruction, and it is assumed that the two groups of diseases represent different entities.

ADDENDUM

After completion of this manuscript the patient was again seen in this department. There had been a recent flare-up in two lesions, and a new lesion had developed on the left upper arm.

Dr. Eleanor M. Humphreys of the Pathology Department and Dr. Stephen Rothman of the Dermatology Section, University of Chicago Clinics, gave advice in the preparation of the manuscript.

CUTANEOUS DIPHTHERIA

Observations on the Primary Pustular Lesion

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IT IS the purpose of this paper to present observations concerning the primary pustular lesions of cutaneous diphtheria. The importance of early recognition of this disease is undisputed. Delay of a week in diagnosis, and consequently in specific treatment, may mean delay of a month in recovery. The pustular lesion has been mentioned previously in the literature, but its importance has not been sufficiently stressed; if recognized it will materially aid the early diagnosis of cutaneous diphtheria.

Concerning the pustular lesion, Livingood and his co-workers [1] said, "It is reasonably certain that the lesions in some individuals had their onset *de novo* in precisely the same manner as an ordinary impetiginous pustule." Cameron and Muir,[2] in discussing acute cutaneous diphtheria, said, "The first clinical sign in such cases was a small blister or pustule centered around a hair follicle; after rupture a flat shallow sore developed with base almost flush with skin and edge composed of skin only . . . " They remarked that these lesions were usually associated with positive nasopharyngeal cultures for diphtheria. The lesions observed healed with little residual change in the skin.

Two cases are presented which illustrate the development of the early pustular lesions of cutaneous diphtheria. They are taken from a collection of 9 cases of cutaneous diphtheria seen at the 97th General Hospital, Frankfurt a. M., Germany, from March 1946 through December 1946.

REPORT OF CASES

CASE 1.—A 19 year old white soldier was admitted to the venereal disease ward on May 2, 1946. A diagnosis of primary syphilis was made on the basis of a penile lesion, which showed Treponema pallida on the dark field. The history revealed no previous venereal disease; the serologic reactions were negative. The physical examination did not reveal complicating factors. Treatment with 4,000,000 units of penicillin was given from May 2 through May 12 with excellent clinical response.

1. Livingood, C. S.; Perry, J. D., and Forrester, J. S.: Cutaneous Diphtheria: A Report of One Hundred and Forty Cases, J. Invest. Dermat. **7**:341 (Dec.) 1946.

2. Cameron, J. D. S., and Muir, E. G.: Cutaneous Diphtheria in Northern Palestine, Lancet **2**:720 (Dec. 19) 1942.

On May 4 a small pustule on the right leg, laterally and just below the knee, was observed. A simple protective dry dressing was applied. The lesion gradually enlarged over a two week period to a lipomatous tumor. It was approximately 7 cm. across; the elevation was about 2 cm. On May 22, the lesion was removed, revealing a clean granulating base. Microscopic examinations showed many bacteria resembling Corynebacterium diphtheriae. Subsequent cultures and smears of the lesion, performed after local treatment had been instituted, were negative. Nose and throat cultures were also negative for C. diphtheriae.

By June 6 the lesion on the leg was healing nicely. However, the patient then had a staggering gait, loss of ocular accommodation, paresthesias of the hands and feet, a positive reaction to the Romberg test and slurring of speech. On June 13 the reaction of the blood to the Kahn test was negative; the spinal fluid examination showed 200 mg. of protein per hundred cubic centimeters and 3 lymphocytes per

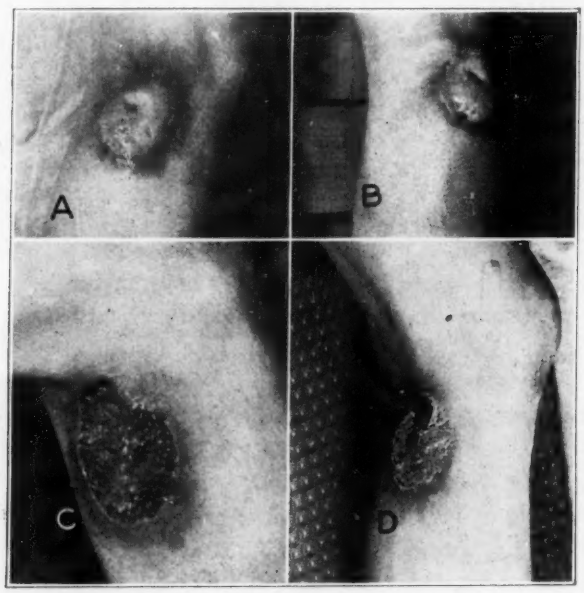

Fig. 1 (case 1).—*A*, appearance of the lesion on May 14, 1946, ten days after its first appearance. It was of the acute type, later ulcerative. (The nose and throat cultures were negative.) *B*, photograph of the ulcer from another view. *C*, appearance of the base of the lesion on May 18. *D*, appearance of the ulcer on June 6, four weeks after onset, in a stage of healing. (Photography by T/4 Robert Gelberg, United States Army Photographic Service.)

cubic millimeter, but no other abnormalities. The sedimentation rate was 11 mm. per hour. The temperature, pulse rate and respiratory rate had remained normal.

A careful review of the history revealed no recent episodes of sore throat or tonsillitis. The patient had been completely well prior to his admission. In his outfit, however, several men had had tonsillitis within a week of this patient's admission. The disease in 1 of these was subsequently diagnosed as diphtheria.

Since it first was thought that the complications might be due to syphilis, penicillin therapy was restarted, in addition to therapy with thiamine 50 mg. daily and supportive measures. Fifty thousand units of penicillin were given every three hours for a total of 2,000,000 units only, since no improvement followed this dosage.

By June 25 there were increasing weakness of the legs and decided weakness of the right deltoid, but ocular accommodation had improved. By June 30 the weakness of the right arm had progressed to involve the deltoids and triceps bilaterally.

Since no rapid improvement could be expected, the patient was transferred to the Zone of the Interior. The final diagnosis was (1) syphilis, primary, new; (2) cutaneous diphtheria, and (3) neuritis, postdiphtheritic, peripheral and central, secondary to the cutaneous diphtheria. The differential diagnosis included the Guillain-Barré syndrome. This clinical entity could be ruled out on clinical

Fig. 2 (case 2).—Acute ulcerative lesion. There are multiple small ulcers at sites of original vesicle formation. (The nose and throat cultures were negative.)

grounds. The development and progression of the neuritis in this case were typical of cutaneous diphtheria.

CASE 2.—A 20 year old white soldier was admitted to the contagious disease section on Nov. 10, 1946. A diagnosis of cutaneous diphtheria was based on the presence of five small ulcers located on the left leg, anteromedial surface, below the knee. These were rounded and punched out, extended through the dermis and were surrounded with approximately 0.5 cm. of erythema. Cultures were taken from the base of the ulcers and were later reported positive for C. diphtheriae, gravis type. Results of virulence studies on guinea pigs were reported positive by the United States Army 4th Medical Laboratory.

Diphtheria antitoxin, 100,000 units, was given immediately, and warm wet dressings were applied continuously. For the first two days the disease process continued. In the immediate surrounding area, groups of small superficial pustules appeared. When the lesions were opened for culturing, a thin white fluid material was revealed. For two days new pustules appeared, despite the presence of continuous wet dressings over the area. These pustules ulcerated to give the clinical appearance seen in figure 2. This patient improved rapidly after the first week. The lesions responded to treatment with continuous warm wet dressings. Later, sulfadiazine paste containing penicillin was used. No complications developed.

COMMENT

From the evidence presented in the 2 cases, it is felt that the pustule may be the initial lesion of primary cutaneous diphtheria. If this is true, then an aid to the early recognition of cutaneous diphtheria has been established. It may be mentioned here that 2 other patients in this group recalled that a pustule had been present early in the course of the disease.

The term secondary cutaneous diphtheria is correctly applied to wound diphtheria. It is also applicable to cutaneous diphtheria when an abrasion or cutaneous lesion was present before invasion of C. diphtheriae. The term primary cutaneous diphtheria should be reserved for the *de novo* diphtheritic infection.

Depending on the cutaneous reaction of the host there would seem to be no reason why the initial pustular lesion should not develop into either the ulcerative or the eczematoid type. The patients reported happened to exhibit ulcerative lesions. While the condition in the second case is illustrative of the more typical lesion, the condition in the first case may reveal the final stage of a diphtheritic pustular lesion when not irritated or treated locally in any manner.

Early recognition of any form of diphtheria is imperative. This is true because the diphtheria antitoxin to be of value must be given within a week of the onset. The value of this therapy decreases with delay. From more than 200 cases of diphtheria [3] observed during the interval mentioned, serious postdiphtheritic complications developed in only 4. All 4 patients had cutaneous diphtheria without clinical evidence of nasopharyngeal diphtheria. None of these received diphtheria antitoxin sooner than four weeks from the onset of the disease. For this reason recognition of the initial pustular lesion of cutaneous diphtheria has been emphasized. A suspicion of diphtheria at the onset of such a lesion may save months of hospitalization for the patient.

SUMMARY

Two cases of cutaneous diphtheria are reported with the initial pustular lesion of the primary type infection. Early recognition of this initial lesion is discussed as an aid to diagnosis of cutaneous diphtheria.

3. Study to be published in the American Journal of Medical Science.

TRANSVERSE NET IN THE DIAGNOSIS OF ONYCHOMYCOSIS

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RELATIVE to the diagnosis of onychomycosis, various features have been described concerning such characteristics as the color and the shape of the nail. However, there exists no clinical feature sufficient in itself to enable one to determine mycotic causation. Microscopic examination with the observation of spores and mycelial threads and growth on culture mediums alone furnish convincing proof for this diagnosis.

In 1939, at the meeting of Polish Dermatologists held in Vilna, Poland, I read a paper on a feature, hitherto unpublished, which makes definite clinical diagnosis possible. This phenomenon does not exist in all cases but when present is pathognomonic. This phenomenon consists of a delicate white net arranged parallel to the transverse axis of the nail. It is visible through a magnifying glass, but only after a drop of cedar oil has been applied. This sign is shown in figure 1. A fragment of this nail, examined under the microscope with partially closed diaphragm, is seen in figure 2. This photomicrograph shows the threads of the net arranged at various levels of the nail plate.

The question of the origin of this net arises. The white threads do not, as might be supposed, correspond to mycelial elements. Examination and measurement in several cases have shown the threads of the net to have a breadth of 10 to 20 microns, while the thickness of mycelial filaments does not exceed 2 to 4 microns.

My histologic examinations of diseased nail plates have convinced me that mycelia grow among the nail cells. Afterward, because of consumption of nail substance, an air space is formed. Thus, after a time, one sees the fungus lying on the bottom of a tunnel 10 to 20 microns wide. It is also rather characteristic that the fungus shows signs of degeneration at this time. It is obvious that what is seen clinically is a network of air spaces within the nail plate.

In view of the transverse direction of the net, one sees only cross sections of the tunnels in longitudinal sections of the nail. Cross sections of nail allow one to visualize the growth of the fungus and development of the air spaces. Figure 3 demonstrates the histologic

From the University of Posen, Poland.

picture of a nail plate showing this transverse net phenomenon. This picture shows the basal layer of the plate which borders on the nail bed (not shown here). Long beads of the fungus can be seen in

Fig. 1.—Transverse white lines due to Trichophyton asteroides.

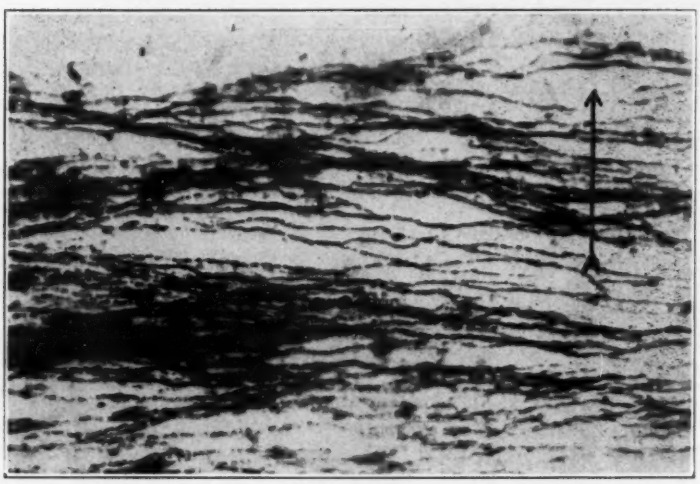

Fig. 2.—The transverse net transilluminated. The arrow indicates the direction of the nail growth.

the chinks between nail tissues. In addition is seen a tunnel 24 microns in width, and on its bottom can be seen fungi showing distinctive features of degeneration.

Having found this sign in several nails after removal, I was encouraged to make further microscopic investigations. I found in that part of the nail proximal to the net, i. e., in the seemingly unaltered nail, a great many mycelial threads visible only under the microscope (magnification 60) and with the diaphragm partly shut. These are the places where fresh growth of fungi occurs, but the air tunnels are not yet produced.

The transverse net is best seen when its constituent threads are not set too close together. When these threads are piled up in layers, an opaque white spot can be seen clinically. Such pictures were described by Ravaut and Rabeau [1] in 1921 and Jessner [2] in 1922. However, on close examination under oil, especially on the border of the spot, the structure of the transverse net can be seen.

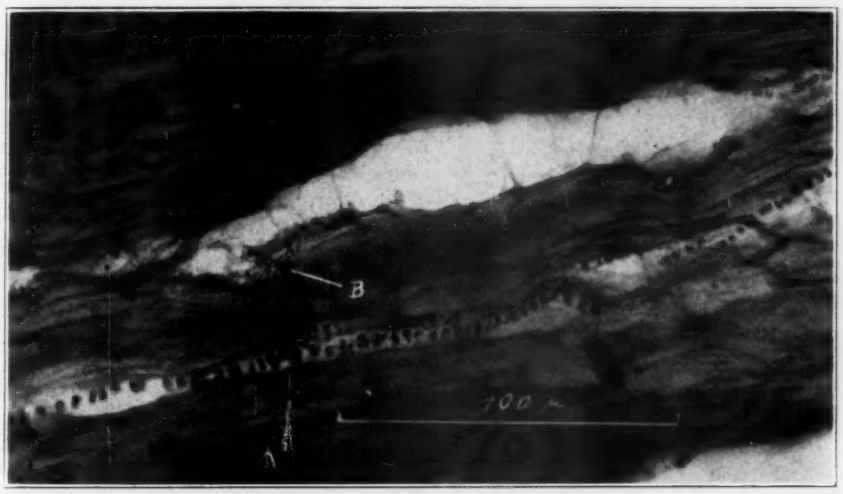

Fig. 3.—Photomicrograph of a transverse section of the nail plate in the case previously illustrated. *A*, mycelium in a chink of the nail substance; *B*, degenerated mycelium in the bottom of a tunnel.

As previously mentioned, this sign of the transverse net does not occur in all cases of onychomycosis, but is evident in a substantial number of them. It is seen most often in trichophytosis of the nails. In favus the sign is seldom encountered. In a case of favus, among eight involved nails, the transverse net was seen in only one.

The net visible in the oil drop grows out simultaneously with the nail and ultimately is shed. This last point would favor a self-limited

1. Ravaut, P., and Rabeau, H.: Sur une forme spéciale de trichophyte unguéale, Ann. de dermat. et syph. **2**:363, 1921.

2. Jessner, M.: Ueber eine neue Form von Nagelmykosen (Leukonychia trichophytica), Arch. f. Dermat. u. Syph. **141**:1, 1922.

disease in onychomycosis. This is obviously not the case, and further investigation reveals the reason. Under the microscope the fungi can be seen to grow in two directions. The transverse type of growth has been described previously. In addition to this, there can be seen in the lower layers of the nail, especially in its longitudinal ridges, fungous growth extending proximally. Figure 4 shows a portion of

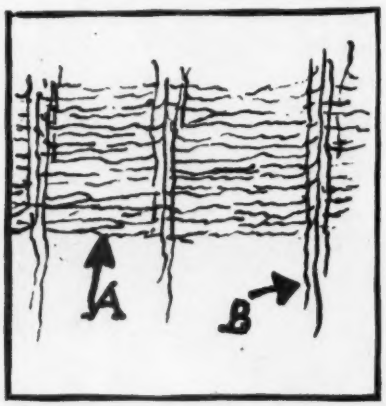

Fig. 4.—A fragment of the nail. *A*, superficial lines are visible (transverse direction). *B*, deeper lines are invisible (proximal direction). The arrow indicates the direction of the nail growth.

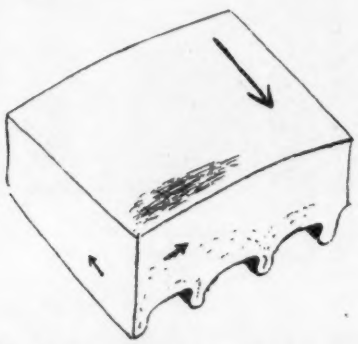

Fig. 5.—Schematic drawing of a segment of the nail plate. The large arrow indicates the direction of the nail growth and the small arrows the direction of the growth of the fungus.

an extracted nail under the microscope and with reduced light. Here are seen numerous transverse threads situated in the upper strata. At right angles to them are seen the longitudinal threads, few in number, the growth of which corresponds to the nail ridges. The former, transverse threads, are visible under clinical observation. The latter are imperceptible in this manner. The schematic drawing, figure 5, shows in what way the fungus grows.

The prognosis of the disease depends on the rapidity with which the fungus invades the longitudinal ridges. If the growth of the fungus remains in equilibrium with the growth of the nail, the disease may persist for years.

My histologic investigations will be published later in more detail. They prove that the fungi grow most of all in the intercellular substance of the nail. The direction of growth depends on the cellular structure in the various parts of the nail plate.

Concerning terminology, I propose the morphologic title "leukopathia unguis mycotica." The term leukonychia should be reserved for the common "gift spots." The etiologic name should be onychomycosis leukopathica.

SUMMARY

A pathognomonic sign of onychomycosis, the transverse white net is described. This phenomenon is visible in the majority of cases of fungous infection of the nail, but only with magnification and through an oil drop. The white lines correspond to air-filled tunnels in the nail plate. Besides these visible transverse spaces there are deeper-laid invisible shafts, extending proximally in the nail ridges. Photomicrographs of a case of onychomycosis due to Trichophyton asteroides are presented and are illustrative of the point.

GRENZ RAY (SUPERSOFT ROENTGEN RAY) THERAPY OF CUTANEOUS DISEASES

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THREE groups of patients with various dermatoses treated with grenz rays (supersoft roentgen rays) are presented in order to compare results with those obtained with conventional, superficial (low voltage) roentgen radiation.[1]

Fifty-eight patients were treated with 76 series of irradiations. A series of irradiations is the exposures given to one patient during any given period. Thirteen patients received more than one series of treatments when first one area and later a second or more areas were irradiated. In these 76 series of treatments, 29 resulted in clearing; 30, in considerable improvement, with almost complete cure; 8 in improvement; 3, in only slight improvement, and 6, in no change (table 1).

The grenz irradiation was produced in a self-rectifying vacuum tube with a thin window of pyrex glass. The electric potentials used were 12 and 14 kilovolts. In grenz ray therapy, however, the thickness of the window acting as a filter determines the quality of the rays

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The grenz ray machine used in this study is manufactured by the X-Ray Manufacturing Corporation of America, New York.

From the Department of Dermatology, New York University College of Medicine, and the Dermatological Service of the Third (New York University) Medical Division, Bellevue Hospital, service of Dr. Frank C. Combes.

1. (*a*) MacKee, G., and Cipollaro, A.: Present Status of Cutaneous X-Ray, Grenz-Ray, and Radium Therapy, Bull. New York Acad. Med. **11**:383 (June) 1935. (*b*) Eller, J. J., and Bucky, G.: The Use of the Grenz-Rays in Dermatologic Conditions, Arch. Dermat. & Syph. **17**:221 (Feb.) 1928. (*c*) Wise, F., and Sulzberger, M.: Grenz-Rays, in the 1935 Year Book of Dermatology and Syphilology, Chicago, The Year Book Publishers, Inc., 1936. (*d*) White, C.: Grenz Rays in Dermatology, Arch. Phys. Therapy **18**:139 (March) 1937. (*e*) Bluefarb, S.: Therapeutic Value of Grenz-Ray in Dermatology, ibid. **25**:400 (July) 1944. (*f*) Ryan, C.: Grenz-Ray Therapy in Dermatology, Brit. J. Dermat. & Syph. **54**:47 (Feb.) 1942. (*g*) Kalz, F.: Theoretic Considerations and Clinical Use of Grenz-Rays in Dermatology, Arch. Dermat. & Syph. **43**:447 (March) 1941. (*h*) Wood, F. C., and MacKee, G.: Therapy with Long Wavelength X-Rays (Grenz Rays), J. A. M. A. **96**:111 (Jan. 10) 1931. (*i*) MacKee, G.: Telangiectasia Caused by Grenz Rays, Arch. Dermat. & Syph. **24**:926 (Nov.) 1931. (*j*) Bucky, G.: Grenz Ray Therapy, New York, The Macmillan Company, 1929.

produced to a greater degree than does the kilovoltage. Accordingly, only the use of half-value layers [2] gives a satisfactory means for comparing the radiation qualities, which in my series of treatments were

TABLE 1.—*Diagnosis and Results of Grenz Ray Therapy in 76 Series of Treatments of Cutaneous Diseases*

Diagnosis	Total Number	Grenz Ray	
		Results *	Number
Acne conglobata	1	—	1
Acne vulgaris	3	+++	3
Dermatitis, contact			
Acute	5	++	1
		++++	4
Subacute	8	+++	6
		++++	2
Chronic	9	++	2
		+++	4
		++++	3
Dermatitis hypostatica	6	++	2
		+++	1
		++++	3
Dermatosis, exudative discoid and lichenoid chronic (Sulzberger and Garbe)	1	++	1
Erythema induratum (Bazin)	1	++	1
Folliculitis, chronic pustular	1	—	1
Granuloma inguinale	1	—	1
Intertrigo	3	+++	2
		++++	1
Lichen planus			
Hypertrophic	1	+++	1
Simple	2	+	1
		+++	1
Neurodermatitis circumscripta	4	+++	3
		++++	1
Neurodermatitis disseminata	3	+++	2
		++++	1
Pain, postherpetic	1	+	1
Pompholyx, with secondary infection	2	+++	2
Pruritus ani	3	+++	1
		++++	1
		—	1
Pruritus ani et vulvae	2	+++	1
		++++	1
Psoriasis	14	+++	1
		++++	13
Sarcoma, ulcerated, Kaposi's	1	+	1
Scar, pruritic	1	—	1
Sycosis vulgaris	1	—	1
Xeroderma, with pruritus	2	++	1
		+++	1
	—	—	—
		—	6
		+	3
		++	8
Total	76	+++	30
		++++	29

* Symbols of results of treatment used in this table, and in the accompanying tables, are as follows: — indicates no change; +, slight improvement; ++, improvement: +++, considerable improvement (almost cleared, but patient was either still under treatment or failed to return for final observation and discharge); ++++ cleared (patient discharged).

0.024 and 0.028 mm. (24 and 28 microns) of aluminum. The half-value layer is that thickness of matter (aluminum in this report) that absorbs 50 per cent of the radiation beam. Except where otherwise noted,

2. (*a*) Kalz.[1g] (*b*) Bucky.[1j] (*c*) Ebbehoj, E.: Untersuchungen über ultraweiche Röntgenstrahlen, ihre Tiefendosiskurven und das Verhältnis zwischen ihren biologischen Wirkungen, Copenhagen, Nyt Nordisk Forlag, 1937.

patients received 100 r doses of roentgen rays at 95 kilovolts weekly and 270 r doses of grenz rays twice weekly.

According to the absorption curves published by Ebbehoj,[2c] approximately 94 per cent of the grenz rays at a half-value layer of 26 microns of aluminum is absorbed in the uppermost 3 mm. of normal skin and practically 100 per cent within the first 5 mm. It is this lack of penetration to the deeper structures which accounts for the safety of grenz rays. This property is recognized by authorities[3] on dermatologic roentgen therapy, who state that grenz radiation is a useful adjunct to roentgen rays in treatment of the eyelids, scalp and scrotum. Early objections to the restricted field of treatment are no longer valid, since the field diameter of the present grenz ray tube is three fourths of the target-skin distance.

Local therapy had been given most patients, with little success, prior to irradiation, and in many instances this local treatment was continued. Only half of the involved area was irradiated in most cases; so bilateral use of local therapy by the patient did not alter the comparative results. This local treatment consisted in the use of a bland emollient or a weak keratolytic ointment; patients with acne received a liquid detergent.

In table 2 are shown the results of grenz ray therapy alone in 27 patients and 29 series of treatments (group A). Nine series resulted in clearing; 8, in considerable improvement; 4, in improvement; 3, in only slight improvement, and 5, in no change.

In group B (table 3) 10 patients received 12 series of treatments, in which roentgen rays were given to the eruption on one side of the body and grenz rays to that on the other side. Two of these patients (cases 29 and 33) had recurrences several months later and were again treated with both forms of radiation. In only 1 series (case 7) were the results of roentgen irradiation better than those of grenz ray therapy; in 6 series the results were similar, while in 5 series grenz rays produced the better results. The duration of treatment with grenz rays was shorter in 2 series (cases 6 and 14), the same in 5 series and longer in 4 series. The duration of treatment in 2 of the last series (cases 29b and 32) was considerably longer because roentgen radiation had been given previously, and a full course of treatment could not be safely administered. Therapy had to be interrupted before healing was accomplished. In both patients, results with the longer course of grenz radiations were much more satisfactory.

Analysis of these 12 series of grenz ray treatments showed that 3 resulted in clearing and 9 in considerable improvement. Roentgen

3. MacKee, G., and Cipollaro, A.: X-Rays and Radium in Treatment of Diseases of the Skin, ed. 4, Philadelphia, Lea & Febiger, 1946.

TABLE 2.—*Results of Grenz Ray Therapy Alone*

TABLE 2.—*Results of Grenz Ray Therapy Alone*

Case and Treatment Number	Diagnosis and Location	Duration	Previous Therapy and Response	Grenz Ray Therapy				Comment
				Area	Time	No. of Doses	Results	
1b	Dermatitis, contact, subacute; both legs	4 mo.	—	Left leg	3 wk.	4	+++	
2b	Dermatitis, contact, acute; both hands and feet	4 wk.	Slight	Right hand and foot	4 wk.	8	++++	
3	Neurodermatitis circumscripta; right foot and right forearm	4 yr.	—	Right foot, left arm	8 wk.	15	+++	
5	Intertrigo; groin	2 mo.	—	Groin, scrotum	2 wk.	4	++	Course not completed
9	Dermatitis, contact, acute; face, neck and left ear	10 mo.	Slight	Face, neck, left ear	4 wk.	11	++++	Local exacerbation
10	Pruritus ani	1 yr.	—	Anus, scrotum	4 wk.	10	—	
11	Acne vulgaris; face	1 yr.	—	Face	20 wk.	14	+++	Course not completed
17	Pain, postherpetic	1 mo.	—	Left side of chest	3 wk.	7	+	350 r
20	Neurodermatitis circumscripta; neck and lower part of back	3 yr.	—	Neck, lower part of back	8 wk.	16	+++	Later new areas of eruption developed
22	Scar, pruritic; face	3 yr.	—	Right cheek	2 wk.	4	—	
24	Pruritus ani	9 mo.	O	Anus	9 wk.	9	++++	Relapse, caused by constipation
27	Lichen planus(?); tongue	7 mo.	— Biopsy specimen (?)	Tongue	6 wk.	6	+	
30	Dermatitis, contact, subacute; face	1 mo.	Slight	Face	2 wk.	5	++++	
36	Sarcoma, ulcerated, Kaposi's	6 yr.	Maximum roentgen ray dose given	Ulcers, right foot	7 wk.	14	+	350 r
37	Pruritus ani	2 yr.	—	Anus	3 wk.	7	+++	
39	Dermatitis, contact, acute; hands	5 mo.	Sensitive to roentgen rays; patch tests negative	Both hands	4 wk.	9	++	
40	Dermatitis hypostatica; right leg	10 yr.	—	Right leg	3 wk.	6	++	
41	Folliculitis, chronic pustular; both forearms	1 yr.	Recurrence	Forearms	2 wk.	4	—	Course not completed
46	Granuloma inguinale	6 yr.	Recurrence	Penis	7 wk.	12	—	450 r
47	Dermatitis hypostatica	7 yr.	Roentgen rays —	Left ankle	8 wk.	16	+++	
48	Sycosis vulgaris	2 yr.	Cleared with 1900 r of roentgen rays	Scalp, face	10 wk.	12	—	Treatment irregular
49	Dermatitis hypostatica	3 wk.	Eruption aggravated	Lower part of legs	10 days	3	++++	150 r
50	Psoriasis; body and scalp	10 yr.	Recurrence	Body, scalp	5 wk.	9	++++	
51	Dermatitis, contact, chronic; hands	2 yr.	Roentgen rays —	Both hands	5 wk.	11	++	Course not completed
54	Acne vulgaris	3 yr.	O	Face, forehead	20 wk.	18	+++	
55	Neurodermatitis disseminata; flexures and groin	6 yr.	Recurrence	Cubital and popliteal fossae, chin	14 wk.	9	++++	180 r weekly
56	Pruritus ani et vulvae	8 yr.	—	Vulva, anus	10 wk.	12	++++	180 r
57a	Pruritus ani et vulvae	8 yr.	—	Vulva, anus	14 wk.	13	+++	190 r
57b	Psoriasis, pubis and elbows	8 yr.	—	Pubis	14 wk.	13	++++	190 r

TABLE 3.—*Results of Roentgen and Grenz Ray Therapy*

Case and Treatment No.	Diagnosis and Location	Duration	Response to Previous Treatment	Roentgen Rays				Grenz Rays				Comment
				Area	Time	Dose	Result	Area	Time	No. of Cases	Result	
1a	Dermatitis, contact, subacute; legs and arms	8 mo.	—	Right arm	4 wk.	5	+++	Left arm	4 wk.	8	+++	Exacerbation, right arm
6	Dermatitis, contact, subacute; both hands	9 mo.	Slight	Right hand	4 wk.	5	+	Left hand	4 wk.	7	+++	Exacerbation, both hands
7	Dermatitis, contact, subacute; hands and feet	1 mo.	—	Right hand, foot	3 wk.	4	++++	Left hand, foot	4 wk.	8	++++	Hospitalization resulted in slight improvement
14	Lichen planus, simple; both legs	2 mo.	—	Right leg	6 wk.	6	++	Left leg	4 wk.	7	+++	350 r 4 times 270 r 3 times Exacerbation, right leg
16	Pompholyx, secondary infection; hands	6 mo.	Slight	Right hand	5 wk.	5	+++	Left hand	6 wk.	7	+++	
18	Acne vulgaris; face.....	8 yr.	—	Right side of face	13 wk.	15	++	Left face	13 wk.	21	+++	Left side of face responded sooner
21	Neurodermatitis circumscripta; both legs	4 yr.	Slight	Right popliteal fossa	4 wk.	4	+++	Left thigh	6 wk.	6	+++	450 r
29a	Intertrigo; breasts.....	7 mo.	—	Right side	2 wk.	3	++	Left side	2 wk.	3	+++	Exacerbation, both sides
29b	Intertrigo; breasts.....	1 mo.	..	Right side	4 wk.	5	++	Left side	12 wk.	9	++++	
32	Pompholyx, secondary infection; hands	6 mo.	—	Right hand	2 wk.	3	+	Left hand	8 wk.	6	++++	
33a	Dermatitis, contact, chronic; arms and legs	6 mo.	++ Hospitalized	Right arm, leg	8 wk.	9	++++	Left arm	8 wk.	12	++++	Left arm responded sooner
33b	Dermatitis, contact, acute; arms and legs	1 mo.	..	Right leg	3 wk.	3	++++	Left arm, knee	4 wk.	4	++++	Exacerbation, 6 mo. later

Case and Treatment Number	Diagnosis and Location	Duration	Response to Previous Treatment	Therapy				Comment
				Area	Time	No. of Doses	Result	
2a	Dermatitis, contact, acute; both hands and right foot	4 wk.	Slight	Left hand	4 wk.	8	++++	Right hand, right foot +
4	Lichen planus, hypertrophic; both legs	4 yr.	—	Left leg	6 wk.	8	+++	Right leg +
8	Psoriasis, scattered	1 yr.	—	Left arm, right leg	6 wk.	13	+++	—
12	Neurodermatitis disseminata, with secondary infection; both arms and hands	2 yr.	Intermittent	Left arm and hand	4 wk.	4	+++	Right arm, right hand +
13	Dermatitis hypostatica; both legs	15 yr.	—	Left leg	5 wk.	10	++	Left leg —; right leg, exacerbation
15	Dermatitis, contact, chronic; both hands	9 mo.	Slight	Left hand	6 wk.	8	++	Right hand +
19a	Xeroderma; right foot and leg	3 mo.	—	Right leg	6 wk.	11	++	Right foot —
19b	Xeroderma; right foot and leg	4½ mo.	—	Right foot	4 wk.	8	+++	
23	Dermatitis, contact, acute; both hands	6 mo.	Intermittent; roentgen ray no benefit	Left hand	8 wk.	14	++++	Right hand +
25	Neurodermatitis circumscripta; cubital fossae	1 yr.	—	Left cubital fossa	4 wk.	5	++++	Right side ++++; slower
26	Erythema induratum (Bazin); both legs	15 mo.	—	Left leg	3 wk.	4	++	Treatment, inadequate response, right leg; —
28	Dermatitis, contact, chronic; both hands	10 yr.	Intermittent	Left hand	6 wk.	8	+++	Right hand; —
31	Dermatosis, exudative discoid and lichenoid chronic (Sulzberger and Garbe); generalized	4 yr.	Intermittent	Left side of chest, left arm	6 wk.	12	++	Right side —; left side, exacerbation several months later
34a	Dermatitis hypostatica, bilateral	18 mo.	—	Left leg	8 wk.	13	++++	Right leg; —
34b	Dermatitis hypostatica, bilateral	19 mo.	—	Right leg	4 wk.	4	++++	
35a	Psoriasis; extremities	3 yr.	—	Left arm	6 wk.	10	++++	Other extremities; —
35b	Psoriasis; extremities	.....	..	Right arm	8 wk.	11	++++	Legs; —
35c	Psoriasis; extremities	.....	..	Both legs	8 wk.	8	++++	
38a	Dermatitis, contact, subacute; hands	1 yr.	—	Right hand	6 wk.	13	+++	Left hand; —
38b	Dermatitis, contact, subacute; hands	.....	..	Left hand	8 wk.	7	+++	
42a	Psoriasis; scalp and body	3 yr.	—	Left side of scalp	18 wk.	17	++++	350 r; irregular treatment
42b	Psoriasis; scalp and body	.....	..	Right side of scalp	12 wk.	9	++++	350 r; irregular treatment
42c	Psoriasis; scalp and body	.....	..	Middle part of back, right anterior thorax	5 wk.	4	++++	190 r; irregular treatment
42d	Psoriasis; scalp and body	.....	..	Left posterior axilla	1 wk.	2	++++	190 r
42e	Psoriasis; scalp and body	.....	..	Lumbar portion of spine	5 wk.	10	++++	190 r
42f	Psoriasis; scalp and body	.....	..	Left midaxilla	1 wk.	2	++++	190 r
43	Acne conglobata	2 yr.	—	Right side of back	8 wk.	12	—	
44	Dermatitis, contact, subacute; face and hands	1 yr.	..	Right side of face, right hand	3 wk.	6	+++	190 r; in hospital 1 mo. previous to treatment
45a	Dermatitis, contact, chronic, lichenified; both thighs	8 mo.	—	Left thigh	3 wk.	7	++++	Local exacerbation
45b	Dermatitis, contact, chronic, lichenified; both thighs	.....	..	Right thigh	12 wk.	19	+++	
52a	Psoriasis; scalp	2 mo.	—	Left side of scalp	9 wk.	16	++++	Right side of scalp; —
52b	Psoriasis; scalp	.....	..	Right side of scalp	5 wk.	9	++++	
53a	Dermatitis, contact, chronic; hands	30 yr.	Intermittent	Left hand	2 wk.	4	+++	Righ hand; —
53b	Dermatitis, contact, chronic; hands	.....	..	Right hand	3 wk.	6	+++	
58	Neurodermatitis disseminata; torso, arms and face	29 yr.	Intermittent	Left side only	4 wk.	8	+++	190 r

irradiation resulted in clearing in 3 series, in considerable improvement in 3 series, in improvement in 4 series, and in slight improvement in 2 series.

In table 4, 22 cases are listed, representing the 35 series in group C in which grenz radiation was given to only one of the involved areas, the remaining areas being used as controls. When the eruption was of equal severity on the two sides, treatment was begun on the left side; otherwise, the area of greater severity was selected.

Of the 35 series of treatments, 17 resulted in clearing, 12 in considerable improvement, 5 in improvement, and 1 in no change. Of the patients with untreated areas, only 1 (case 25) was healed with topical applications and 5 showed slight improvement. Eight series of irradiations were given to the remaining eruption after the initially irradiated areas had been cleared. These, therefore, could no longer be compared with an untreated area.

CASES OF SPECIAL INTEREST

CASE 2.—The patient was first seen with lesions of pruritic, weeping, vesicular, erythematous contact dermatitis on both hands and the dorsum of the right foot, all of which had been under treatment with compresses and bland ointments for four weeks. Two exposures of grenz rays to the left hand was followed by such improvement that the emollient-fixed dressing was discontinued, but only on that hand. In two weeks, after four treatments, the subjective and objective difference between the two hands was remarkable. In four weeks the left hand was healed, while the right hand and foot were eczematized and fissured, despite the continuous use of a fixed dressing. At this time, grenz ray therapy was begun on these areas, which were symptomatically relieved in two weeks and cured in six weeks.

CASE 31.—A patient with exudative discoid and lichenoid chronic dermatosis (Sulzberger and Garbe) of four years' duration was given twelve exposures to the left arm and the left side of the thorax. Despite obvious objective improvement, with drying and healing of the patches on the left side only, the patient complained of continued pruritus. He showed no evidence of excoriation, however, and therapy was discontinued.

CASE 35.—A patient with psoriasis en plaque involving all extremities had made no response to local therapy for three years. Grenz radiation was given to the left arm. When the eruption in this area cleared, the right arm, and later the legs, were treated. Each area cleared independently after it had received about ten exposures within five to six weeks. The areas treated showed moderate hyperpigmentation, which disappeared after about two months. Ten months later, a check showed that no relapses had occurred.

CASE 42.—A patient with guttate psoriasis of the trunk and scalp and two large plaques over the lumbar portion of the spine was treated with grenz rays in six series. The scalp was irradiated for eighteen weeks. The itching was rapidly relieved, and the lesions finally cleared completely. The guttate lesions of the thorax were treated in four groups, and each cleared independently after two to four treatments. No lesions had recurred when the patient was discharged, five months later.

CASE 55.—A girl aged 6, with neurodermatitis disseminata involving the flexures, groins and face, received one field of exposure on the cubital areas, which cleared after three to four treatments. Here the eruption persisted just above and below the 6 inch (15 cm.) field. Treatment of the skin above and below the elbow in two fields resulted in healing of the entire area. The eruption on other areas not then treated persisted until treated later.

CASE 58.—A patient with neurodermatitis disseminata involving the entire body above the waist was given grenz rays on the left side only. On the abdomen and chest, the eruption and pruritus cleared within the circle of the exposed field only. There was considerable hyperpigmentation of the skin prior to irradiation; the pigmentation was increased in the areas after grenz ray therapy.

SUMMARY

Seventy-six series of treatments with grenz rays of 58 patients produced the following results: Twenty-nine resulted in clearing; 30, in considerable improvement; 8, in improvement; 3, in slight improvement, and 6, in no change.

Patients with twenty diseases of the skin represented in this report were sent in for treatment from the general dermatologic clinic after their failure to respond satisfactorily to local therapy.

Three methods of therapy were presented; (*a*) use of grenz rays (supersoft roentgen rays) only; (*b*) treatment of one half of the eruption with roentgen and of the other half with grenz rays; (*c*) grenz ray treatment of only one half the area involved.

Several case histories of special interest are reported.

CONCLUSIONS

1. The 76 series of treatments with grenz rays (supersoft roentgen rays) show results which compare favorably with published reports of diseases of the skin treated with roentgen rays.

2. In the group in which both modalities of radiation were given the same patient, the results were slightly in favor of the grenz rays.

3. Treatment of grenz rays with a half-value layer of 0.028 mm. (28 microns) or less of aluminum appears to be a safe form of physical therapy.

4. Grenz ray therapy is especially useful for superficial diseases of the skin. Controlled treatment eliminates the possibility of a psychotherapeutic effect in those diseases in which such an effect might occur.

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RECURRENT HERPETIFORM DERMATITIS REPENS

Report of a Case

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THE LITERATURE on this comparatively new entity, first described by Ayres and Anderson under this name,[1] has been summarized recently by Sachs, Hyman and Gray.[2] Although Pels and Goodman [3] were probably the first to describe this condition, they regarded it only as a variant of Darier's disease (keratosis follicularis). Priority has been accorded to Hailey and Hailey,[4] who were the first to consider this disease as a dermatologic entity. There is, however, no agreement on the classification of the disease, and thus a considerable number of names have been suggested. While observers agree on the identity of the clinical course and picture of this disease, the interpretation of the peculiar histologic features is still under discussion. This situation seems to warrant the publication of a case which I had the opportunity to observe.

REPORT OF CASE

M. G., a married white woman aged 31, was first seen on Nov. 28, 1945 at the Cedars of Lebanon Hospital, Los Angeles. The patient complained of a recurrent eruption of eight years' duration on the upper part of her back and her shoulders. No information as to the presence of similar lesions in other members of her family was available. The patient complained of no symptoms other than the eruption, which was decidedly pruritic. The personal history was essentially noncontributory.

Physical Examination.—The patient was a well developed, healthy-appearing white woman. General examination revealed no pathologic changes other than the lesions in the skin.

Skin: On the outer side of the upper part of the left arm there was an irregularly ovoid lesion about 2 inches (5 cm.) in diameter. The lower part of this lesion consisted of grouped, crusted elevations and exhibited a sharply demarcated, somewhat circinate, elevated border, which in its upper portion was composed of unbroken vesicles. There was evident, though hardly visible, a

1. Ayres, S., Jr., and Anderson, N. P.: Recurrent Herpetiform Dermatitis Repens, Arch. Dermat. & Syph. **40**:402 (Sept.) 1939.

2. Sachs W.; Hyman, A. B., and Gray, M. B.: Epidermolysis Bullosa: A Recent Described Variant, Arch. Dermat. & Syph. **55**:91 (Jan.) 1947.

3. Pels, I. R., and Goodman, M. H.: Criteria for the Histologic Diagnosis of Keratosis Follicularis (Darier), Arch. Dermat. & Syph. **39**:438 (March) 1939.

4. Hailey, H., and Hailey, H.: Familial Benign Chronic Pemphigus, Arch. Dermat. & Syph. **39**:679 (April) 1939.

circinate, hourglass-like configuration of the upper part of the border, which extended in an upward direction; it was occasionally accentuated by remnants of crusted papules. The center of the lesion was depressed and pinkish (fig. 1). The eruption on the patient's back showed a peculiar combination of pigmentation and depigmentation and two lesions clinically similar to those on the upper portion of the arm. In the right axilla there was an ill defined crusted patch extending toward the chest in a broad band; this represented remnants of a larger lesion, which had left pigmentation on involution.

Course.—A biopsy specimen was taken from the lesion on the back on December 26. One roentgen ray treatment (75 r, unfiltered) was given to all the lesions on Jan. 2, 1946. There was steady improvement, and on February 20 the areas were completely cleared.

Laboratory Studies.—A blood count showed 4,000,000 erythrocytes, 73 per cent (12.3 Gm.) hemoglobin, a color index of 0.91, 76 polymorphonuclear leukocytes, 15 lymphocytes, 2 eosinophils and 7 monocytes.

Fig. 1.—Lesion on the upper portion of the left arm, showing the elevated, circinate lower border, composed of unbroken vesicles and crusts.

The reactions to the Kline and Wassermann tests were negative. The specific gravity of the urine was 1.026, and the reactions for sugar and albumin were negative.

Biopsy.—Slides were sent to the Army Institute of Pathology, Washington, D. C., on Feb. 9, 1946, by the Department of Pathology of the Cedars of Lebanon Hospital.

Report of Army Institute of Pathology: Gross Appearance: The biopsy specimen, which consisted of an elliptic segment of skin, measuring 16 by 5 mm., had been fixed in Bouin's fluid (Path. Accession No. 161561). Nothing characteristic was observed grossly.

Sections were prepared from two areas.

Microscopic Appearance: An examination of numerous serial sections revealed stratified squamous epithelium, which was only slightly thicker than normal. There were slight parakeratosis and keratosis. The granular cell layer was slightly thicker than normal. Occasionally intraepithelial vesicles filled with inspissated, amorphous material and numerous leukocytes, chiefly polymorphonuclear, were seen.

There were numerous irregular defects in the malpighian layer. These defects were partly filled with amorphous and granular, pink-stained material, containing a few polymorphonuclear leukocytes, as well as round cells. A few desquamated epithelial cells could be seen. These were fairly well preserved in a few areas. However, there were many minute acidophilic granules in the intracellular layers; some of these lay within the cells and may have represented inclusion bodies. The papillae were relatively blunt. In the papilla or superficial portion of the corium the capillaries were numerous and moderately dilated and showed moderate perivascular infiltration with round cells. Some of these round cells were

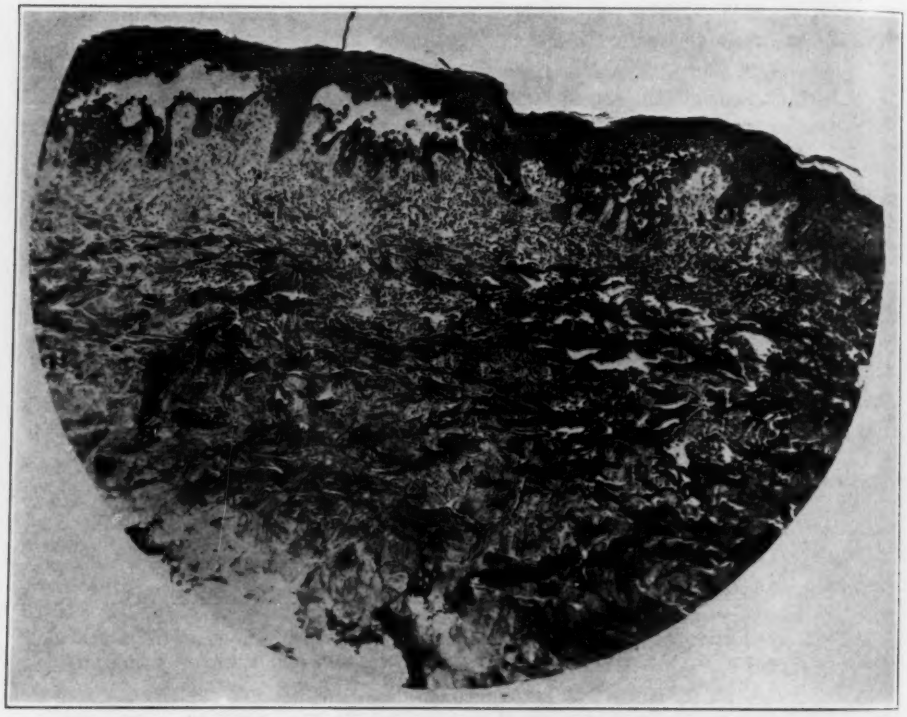

Fig. 2.—Low power photomicrograph, showing hyperkeratosis, a thickened granular layer and formation in the prickle cell layer of clefts containing round epithelial cells. To the right are finger-like projections of rete pegs, containing loose, disorganized, rounded prickle cells.

identified as lymphocytes; others were large and resembled macrophages. Some of the latter were elongated, and the endothelial cells of the blood vessels were plump.

Diagnosis: The disease was diagnosed as keratosis follicularis.

Personal Report: Before I received the report of the Army Institute of Pathology, I recorded my own histologic observations as follows:

The predominant pathologic changes were those present in the epidermis. The prickle cell layer exhibited numerous clefts with fiordlike, irregular borders. These clefts were situated in the lower part of the epidermis. The roof, therefore, was made up of a number of rows of prickle cells of apparently normal appearance, while the base was frequently represented by a single layer of basal cells. This was true of the majority of the clefts, except for some very large ones, which seemed

to occupy almost the entire thickness of the epidermis. However, the lower border of even the largest clefts was always formed by a row of basal cells. These lacunas were numerous, so much so that some were separated from one another only by small bridges of normal epidermis. Sometimes they were also seen in the broadened rete pegs. Some cells, adjacent to the clefts, seemed to be in irregular positions in relation to one another. In these cells the prickles were apparently absent, thus causing the loss of their physiologic device for regularity. Most of the clefts contained rounded, loose epidermal cells, which were scattered

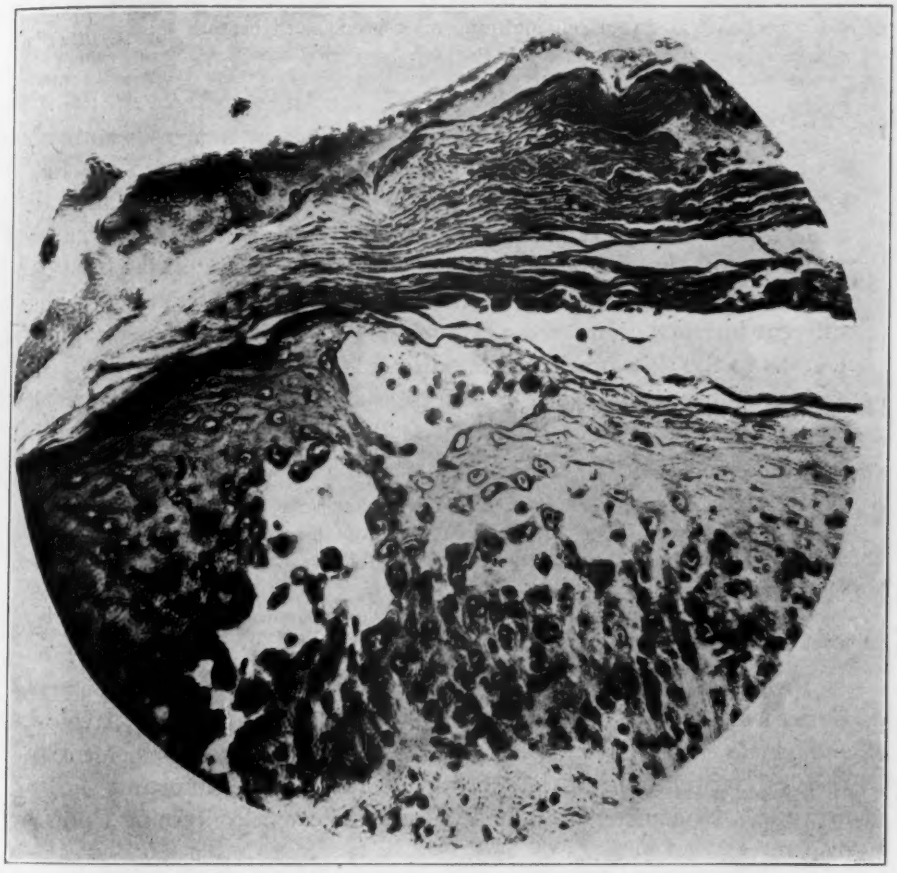

Fig. 3.—High power photomicrograph. Hyperkeratosis and parakeratotic scale are shown; the granular layer is absent. In the center is a subcorneal abscess containing round cells and detritus. Formation of lacunas in prickle cell layer and acantholysis are shown.

about like dice on a table. These cells could be recognized as rounded prickle cells which had lost their prickles. Occasionally eosinophilic staining of their cytoplasm was noticed. However, the nuclei were well stained and preserved, and the nucleoli were plainly visible. In addition, there were a few small abscesses in the upper part of the epidermis directly beneath the corneal layer; these were filled with leukocytes and cell detritus. The number of rows in the basal cell layer,

particularly below the clefts, was increased; mitotic figures were noticeable. Acanthosis, due partly to the proliferation of the basal cell layer, was present. The junction of the epidermis and the corium was straight in some places, whereas in others, particularly in the region of the lacunas, there were finger-like projections of the rete pegs.

The horny layer was moderately thickened and contained serum, fibrin and, occasionally, round cells and detritus. Above the site of the clefts the granular layer was either increased in size or missing. In those places where it was missing a parakeratotic scale was present, representing probably a later phase of development. The upper portion of the cutis was the site of dilated vessels and a perivascular round cell infiltrate, most pronounced beneath the site of the epidermal lacunas (figs. 2 and 3).

COMMENT

The clinical picture of the disease, as described by numerous authors, has been fairly well established. The outstanding features are (1) formation of vesicles or bullae, with subsequent rupture and formation of crusted lesions, and (2) response to superficial roentgen irradiation within a short time. The clinical features seem to justify a classification of the disease as vesicular dermatitis. It is, however, due largely to the different interpretations of the histologic features that there is disagreement as to the classification of the disease.

One entity to which this disease has histologic resemblance is Darier's disease (keratosis follicularis). Ehrmann [5] described Darier's disease as follows:

> . . . A rare disease, sometimes traceable through two or three generations, [it is] characterized by a formation of dull papules, reddish in the beginning, which are sometimes located on top of the follicles. Soon they develop into flat or bluntly conical, earth-colored papules, which rub off easily, as they consist mainly of horny material. By confluence of papules, flat plateaus develop, which are rough, slightly verrucous and earth colored.

Brunauer [6] stated that the completely developed, typical lesion of Darier's disease is a small papule, covered with a horny scale. Atypical, and chiefly secondary to the primary lesion, is the development of vesicles, pustules, urticarial eruptions and lesions simulating lichen urticatus. Brunauer [6] made the following statement concerning Darier's disease:

> The disease is fundamentally a progressive one; while remissions and exacerbations occur, there is a tendency toward gradual progression. The disease sometimes lasts from early youth to old age. It is hardly, if at all, influenced by any form of therapy.

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5. Ehrmann, S.: Die Psorospermosis cutis, Keratosis follicularis (Darier), in Vergleichend-diagnostischer Atlas der Hautkrankheiten und der Syphilide, Jena, G. Fischer, 1912.

6. Brünauer, St. R.: Ueber Hauterscheinungen bei Morbus Darier, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1927, vol. 8, pt. 2.

On the basis of histologic studies, Sachs, Hyman and Gray [2] recently attempted to show that the disease is not pemphigus, dermatitis herpetiformis or Darier's disease, but a form of epidermolysis bullosa. Incidentally, Ayres and Anderson [1] would not give the name "herpetiform

Comparative Histologic Features of Darier's Disease, Epidermolysis Bullosa and the Presented Disease

Histologic Change or Structure Involved	Darier's Disease	Epidermolysis Bullosa	Presented Disease
Stratum corneum	Considerably enlarged; follicular horny plugs present	Thinner than normal, as a rule	Moderately thickened
Parakeratosis	Present	Present	Present
Stratum granulosum	Considerably thickened in spots	Normal	Thickened in spots
Prickle cell layer	Considerably thickened	Thin, two layers as a rule	Thickened
Basal cell layer	Considerably thickened; very active, sometimes resembling pseudoepitheliomatous hyperplasia	Normal	Thickened; proliferating mitotic figures
Pigment	First increased, later diminished; dendritic melanoblasts adjacent to clefts	Increased in bullae of long standing	Normal
Epidermodermal junction	Finger-like projections of basal cell layer into the rete	Normal	Normal in spots; finger-like projections of rete pegs in other areas
Superficial abscess (subcorneal)	Absent	Sometimes present (Siemens, H. W.: Arch. f. Dermat. u. Syph. **134**: 454, 1921)	Always present
Lacunas or clefts in epidermis	Present	Present	Present
Location of lacunas	Within epidermis; lower border always formed by basal cell layer	Mostly between cutis and epidermis; lower border formed by papillary layer	Within epidermis; lower border always formed by basal cell layer
Content of lacunas	Considerable amount of corps ronds, grains (dyskeratosis) and detritus	Amorphous material, fibrin, erythrocytes, leukocytes, nuclei, eosinophils, epidermal cells (Blumer, C., cited by Brünauer [6])	Rounded prickle cells, sometimes resembling corps ronds, pseudodyskeratosis (Sachs [2]), or dyskeratoid dermatosis of Frank and Rein [11]
Cutis	Perivascular infiltrate, mostly lymphocytes, occasionally leukocytes and eosinophils; elastic fibers normal	Moderate dilatation of papillary vessels and lymph capillaries; perivascular infiltrate; elastic fibers degenerated or missing (dystrophic form)	Dilatation of papillary vessels, perivascular infiltrate; elastic fibers normal

dermatitis" to this disease because of a resemblance to Duhring's disease. They stated:

> Because of its resemblance to dermatitis repens and to herpes simplex, we have suggested the name "recurrent herpetiform dermatitis repens."

The accompanying table is presented to show the histologic similarities and differences of Darier's disease, epidermolysis bullosa (according to Brünauer [6] and Riecke [7] and the disease presented (table).

7. Riecke, E.: Epidermolysis bullosa, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1927, vol. 7, pt. 2.

Recently a case of bullous dyskeratosis ("familial benign chronic pemphigus") was presented by Miller and Rees [8] before the San Francisco Dermatological Society. In the discussion, Templeton [9] pointed out that the histologic picture was classic and could be substituted for one of the illustrations in the original description of the disease. Another case of benign familial pemphigus was presented by Lynch [10] before the Minnesota Dermatological Society. In both these cases the diagnosis was accepted without controversy. Many other cases of this condition, under various names, have been reported in the last eight years, recognizable by distinct clinical and histologic features. These citations indicate that, in spite of its many similarities to other diseases, this dermatosis has distinct and characteristic features which permit an undisputed diagnosis in typical cases. I am fully in accord with the following statement by Frank and Rein,[11] which expresses an opinion shared by Montgomery,[12] Anderson [13] and others.

> We are fully aware of the many similarities that would suggest a relation to pemphigus, Darier's disease and dermatitis herpetiformis, as has been suggested by other authors. However, it is our contention that there is not enough similarity to allow for such a point of view at present. The condition presents a definite clinical and microscopic picture that justifies its consideration as a separate entity until further observations are able to place it in a definite category.

SUMMARY AND CONCLUSION

A case of bullous dermatosis described by Ayres and Anderson [1] as "recurrent herpetiform dermatitis repens," and by others under various names, is presented.

Clinical and histologic similarities and dissimilarities between this disease and other diseases, which may be considered in the differential diagnosis, are discussed.

Until further evidence has been submitted to the contrary, it appears justifiable to consider the described condition as a distinct and separate clinical and histologic entity.

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8. Miller, H. E., and Rees, B.: Bullous Dyskeratosis (Familial Benign Chronic Pemphigus), Arch. Dermat. & Syph. **55**:730 (May) 1947.

9. Templeton, H. J., in discussion on Miller and Rees.[8]

10. Lynch, F. W.: Benign Familial Pemphigus, Arch. Dermat. & Syph. **56**:134 (July) 1947.

11. Frank S. B., and Rein, C. R.: Dyskeratoid Dermatosis, Arch. Dermat. & Syph. **45**:129 (Jan.) 1942.

12. Montgomery, H., in discussion on Frank and Rein,[11] p. 148.

13. Anderson, N. P., in discussion on Frank and Rein,[11] p. 148.

ALLERGIC CONTACT DERMATITIS DUE TO RUBBER

With Special Reference to Latex

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THE IMPORTANCE of rubber as a cause of dermatitis both in its manufacture and use has received due emphasis in the literature. Schwartz, Tulipan and Peck [1] have written extensively on the occupational disease hazards to the skin in the manufacture of both synthetic and natural rubber. In a recent article [2] on dermatitis due to wearing apparel, Schwartz and Peck reviewed the literature and found rubber gloves, girdles, dress shields, gas masks and condoms among the commoner rubber sensitizers. Other rubber goods, such as bunion protectors,[3] ear phones,[4] art gum erasers,[5] rubber tips of stethoscopes,[6] friction tape,[7] adhesive tape,[8] rubber fillers in eyelash curlers [9] and rubber cement used in the manufacture of shoes [10] have been reported as proved causes of dermatitis. In our own practice, we have seen 33 proved cases of dermatitis due to rubber. These were due to rubber gloves,[10] rubber dress shields,[2] rubber guards over ear pieces of glasses,[3] condoms,[2] elastic in hose, rubber cable, rubber baby pants and miscellaneous rubber materials.

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1. Schwartz, L.; Tulipan, L., and Peck, S. M.: Occupational Diseases of the Skin, ed. 2, Philadelphia, Lea & Febiger, 1947, p. 498.

2. Schwartz, L., and Peck, S. M.: Dermatitis from Wearing Apparel, J. A. M. A. **128**:1209-1217 (Aug. 25) 1945.

3. Niles, H. D.: Dermatitis Due to Rubber Bunion Protector, J. A. M. A. **97**:778 (Sept. 12) 1931.

4. Thomas, R. B., and Smith, T. W.: Report on Sensitivity to Rubber Earpieces on Headphones, Air Surgeon's Bull. (no. 5) **1**:11 (May) 1944.

5. Adkinson, J., and Walker, I. C.: A Patient Sensitized to Art Gum Eraser, J. A. M. A. **101**:2117-2118 (Dec. 30) 1933.

6. Halloran, C. R.: Contact Dermatitis Due to Rubber Tips of Stethoscope, Arch. Dermat. & Syph. **36**:140-141 (July) 1937.

7. Schwartz, L., and Albaugh, R. P.: Dermatitis in Nut and Bolt Plant Due to Use of Friction Tape, Pub. Health Rep. **49**:1051-1056 (Sept. 7) 1934.

8. Schwartz, L., and Peck, S. M.: Irritants in Adhesive Plaster, Pub. Health Rep. **50**:811-819 (June 14) 1935.

9. Curtis, G. H.: Contact Dermatitis Caused by an Anti-Oxidant in Rubber Fillers of Eyelash Curlers: Report of Seven Cases, Arch. Dermat. & Syph. **52**:262-265 (Oct.) 1945.

10. Gaul, L. E.: Personal communication to the authors.

REPORT OF TWO CASES

CASE 1.—Mrs. M. B., white woman, aged 25, was first seen in March 1942, complaining of a severe eruption in the axillas that followed the wearing of a pair of dress shields. She gave a history of having a weeping eruption of the dorsa of her feet the previous summer, which she attributed to the rubber straps of her bathing sandals. The patient presented an extensive, severe, erythematous weeping and vesicular dermatitis in both axillas. Patch tests were made with the cloth on the dress shields as well as with the rubber lining, and both resulted in a 3 plus reaction. The patient was again seen in 1945, at which time she presented an extensive weeping vesiculobullous dermatitis involving the hands, wrists and forearms and to a lesser extent the arms, neck and face. The eruption appeared within twenty-four hours after she had worn a pair of synthetic rubber gloves and was so severe that she was incapacitated for two weeks. She had first inflated the gloves by blowing into them and wore them for only ten minutes. In July 1945 there appeared across the dorsal surface of each foot a bandlike group of vesicles after she had worn a new pair of play shoes. About a year later, after she had worn a pair of sandals, this same picture was reproduced, with the addition of acute vesiculation of the soles.

The manufacturer of the rubber gloves in question was contacted in an attempt to determine the sensitizing agent. She was tested with six samples of synthetic rubber, and, although she was found to be sensitive to three, we were unable to determine from these tests the exact offending ingredient. Since then, we learned from our patient that she was able to use rubber gloves made of neoprene® (a polymer of chloroprene, a synthetic derivative of acetylene) latex from another manufacturer without difficulty. The result of a patch test to a crude neoprene® (synthetic) latex® was negative.

CASE 2.—Mrs. C. Z., a white woman aged 35, was observed with an acute generalized eruption, which first appeared and was worse on the flexor surface of the forearms. There was also extensive involvement of the arms, neck and face. The eruption was a diffuse edematous nonvesicular dermatitis which appeared two weeks before she was observed by us. She attributed her symptoms to a permanent wave which she had received a day prior to the onset of the eruption. This was ruled out because the scalp was entirely free. No definite history of other allergenic contactants could be elicited. A striking feature was the complete bilateral symmetry of the acute edematous and erythematous noneczematous eruption of the flexor surfaces of the forearms, which stopped abruptly at the cubital spaces. A week of soothing therapy produced only slight improvement. After much discussion, because the location of the eruption suggested irritation from holding her baby, a patch test was made with her baby's rubber pants, which caused a 3 plus reaction. The patient then recalled that at the time of the onset of the eruption she had changed the brand of her baby's pants, because she was unable to obtain the type ordinarily used. After discarding the offending brand of rubber pants, recovery was rapid and complete.

According to the label, the incriminated rubber pants were manufactured from "creamy neoprene latex." Several attempts were made to obtain the ingredients used in the manufacture and processing of this rubber in order to trace the offending material, but the manufacturer was uncooperative. Subsequently, patch tests were performed with four other brands of pink baby pants made of synthetic latex, including the type the patient used without difficulty. Tests with the latter brand gave negative reactions while tests with the other three gave 1, 2 and 3 plus reactions, respectively.

COMMENT

According to Schwartz and his co-workers,[1] up to 1926 dermatitis due to rubber was prevalent, but since then the number of cases has materially diminished because many rubber manufacturers have discontinued the use of well known irritating accelerators and antioxidants.

During World War II, the manufacture of synthetic rubber was begun on a large scale in this country. Its widespread use had undoubtedly caused many cases of dermatitis. However, scant reference has been made in the literature to specific cases of dermatitis produced by synthetic rubber.

Most of the dermatitis produced in the users of rubber goods is probably the result of handling the latex form of rubber from which are manufactured gloves, all-rubber girdles, condoms and similar articles. Synthetic latex, according to Schwartz and his co-workers,[1] is more likely to cause dermatitis, because, in addition to the accelerators, antioxidants and other compounds used in the processing of both synthetic and natural rubber, the former also contains more uncombined and unpolymerized chemicals. In natural rubber these antioxidants and accelerators were long known to be the actual cause of the dermatitis, rather than the rubber itself. In addition to these chemicals, in synthetic rubber "something new" has been added. However, we did patch tests in 5 of our cases in which there was sensitivity to rubber with crude neoprene® (synthetic) latex® obtained from the Dupont company, which gave negative results.

Among the difficulties encountered in tracing the irritating ingredient in rubber, natural or synthetic, is the fact that many rubbers are "vapor cured" with sulfur monochloride. With this method of processing, according to Schwartz and his co-workers,[1] compounds are formed continuously on the surface of the rubber, and these compounds may be the irritants or sensitizers. In addition, in some rubbers the accelerators are incorporated loosely and are leached out by perspiration or, when contained in too large a quantity, "bloom out," whereas ordinarily they could cause no trouble.

To learn the specific offending substance, Schwartz and his co-workers[1] stated, ". . . the rubber may be traced to the factory and information can be obtained concerning the accelerators, anti-oxidants and other compounds in the rubber. Patch tests with these substances usually reveal the irritant." From our experience, it is not as simple as herein stated not only because of the poor cooperation of the manufacturers but also because of the "leaching and blooming out" processes described herein and the irritating or sensitizing compounds that may be continuously formed on the surface of certain "vapor-cured" rubbers.

The cases of dermatitis herein reported were specifically caused by synthetic rubber. In the first case, the cause was readily apparent and was produced at the slightest contact with different types and forms of rubber. Blowing into a pair of rubber gloves, for example, produced an extensive and severe dermatitis of the face. In the second case, the offending agent was not so evident. A casual and entirely unsuspected article was at fault. On thorough questioning, the patient stated that she "did nothing" which could possibly cause her dermatitis, a phrase one hears so often in trying to trace dermatitis-producing contactants. Here, an article of wearing apparel produced no dermatitis in the wearer, i. e., the baby, but did cause a severe and extensive eruption in an innocent (but interested) bystander.

SUMMARY

Two cases of extensive dermatitis due to contact with synthetic rubber are reported. In 1 case the hypersensitivity due to rubber was so severe as to incapacitate the patient at the slightest contact, while in the second case, "detective work" was necessary in uncovering latex baby pants as the cause of dermatitis in a mother. Unsuccessful attempts were made to trace the offending ingredients in both cases, but this quest is difficult because of the complexity of synthetic rubber, certain rubber processing methods and unwillingness of the manufacturers to cooperate fully with investigators.

GENETICS OF XANTHOMA TUBEROSUM MULTIPLEX

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THE PRIMARY essential xanthomatoses have been divided by Thannhauser and Magendantz,[1] Montgomery [2] and others on the basis of the clinical picture and the fat content of the blood. The xanthoma tuberosum type with which this paper will concern itself is characterized by hypercholesteremia and a tendency to xanthomatous involvement of the skin, tendon tumors and, of much graver consequence, early cardiovascular disease.

Although the familial occurrence of this condition has been recognized by many observers [3] since its description in 1851 by Addison and

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From the Departments of Dermatology and Syphilology and Internal Medicine, University of Michigan Medical School, and the Heredity Clinic of the Laboratory of Vertebrate Biology, University of Michigan.

1. Thannhauser, S. J., and Magendantz, H.: The Different Clinical Groups of Xanthomatous Diseases: A Clinical Physiological Study of Twenty-Two Cases, Ann. Int. Med. **11**:1662, 1938. Thannhauser, S. J.: Lipoidoses: Diseases of the Cellular Lipid Metabolism, New York, Oxford University Press, 1940.

2. Montgomery, H.: Cutaneous Manifestations of Diseases of Lipoid Metabolism, M. Clin. North America **24**:1249, 1940.

3. (*a*) Montgomery.[2] (*b*) Wilks, cited by Fagge, C. H.: Two Cases of Vitiligoidea Associated with Chronic Jaundice and Enlargement of the Liver, Tr. Path. Soc. London **19**:434, 1868. (*c*) Mackenzie, S.: Two Cases of Congenital Xanthelasma, ibid. **33**:370, 1882. (*d*) Török, L.: De la nature des xanthomes (avec quelques remarques critiques sur la nature des tumeurs), Ann. de dermat. et syph. **4**:1109, 1893. (*e*) Morichau-Beauchant and Bessonnet, R.: Le xanthome héréditaire et familial, Arch. gén. de méd. **192**:2313, 1903. (*f*) Gossage, A. M.: The Inheritance of Certain Human Abnormalities, Quart. J. Med. **1**:331, 1908. (*g*) Beeson, B. B., and Albrecht, P. G.: Contribution to Study of Xanthoma Tuberosum, Arch. Dermat. & Syph. **8**:695 (Nov.) 1923. (*h*) Fasold, A.: Studien über Vererbung von Hautkrankheiten: VI. Xanthom (Cholesterosis cutis), Arch. f. Rassen- u. Gesellsch.-Biol. **16**:54, 1924. (*i*) Grenaud, M.: Les xanthomes familiaux, Thesis, Paris, Jouve & Cie, 1927; Monde méd., Paris **37**:725 (Aug. 1) 1927.

Gull, Török [3d] was apparently the first to emphasize the hereditary nature of the disease. In the intervening years there have been several excellent reviews and reports touching on the genetic problems involved. The conclusions drawn have been of a conflicting nature, and the authors may be divided into several groups: (*a*) those [4] who stated the belief that the mode of inheritance of xanthoma tuberosum multiplex was as a single dominant characteristic, (*b*) some [5] who expressed the opinion that it was an irregular dominant characteristic, (*c*) others [6] who stated that it was a recessive characteristic, (*d*) a group [7] who expressed the opinion that the abnormality inherited was the disturbance in the cholesterol metabolism rather than in the xanthomatous deposits and (*e*) one [8] who postulated two different genetic factors, one for the hypercholesteremia and the other for the deposits themselves.

For many years investigators [9] have recognized the frequent association of xanthoma tuberosum with angina pectoris, coronary sclerosis, occlusive vascular disease of the extremities, arcus senilis or gallbladder disease. These observations have properly prompted several investi-

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4. Török.[3d] Müller, C.: Angina Pectoris in Hereditary Xanthomatosis, Arch. Int. Med. **64**:675 (Oct.) 1939.

5. (*a*) Fasold.[3h] (*b*) Lane, G. C., and Goodman, J., Jr.: Xanthoma Tuberosum: Report of Familial Occurrence with Probable Cardiac Lesions, Arch. Dermat. & Syph. **32**:377 (Sept.) 1935. (*c*) Lapowski, B.: Familial Xanthoma: Tuberosum Multiplex in Two Sisters, ibid. **11**:701 (May) 1925.

6. Levin, E. A., and Sullivan, M.: Familial Xanthoma, Arch. Dermat. & Syph. **33**:967 (June) 1936. Thannhauser, S. J., and Schmidt, G.: Lipins and Lipidoses, Physiol. Rev. **26**:275, 1946.

7. Lane and Goodman.[5b] Lapowski. [5c] Sperry, W. M., and Schick, B.: Essential Xanthomatosis: Treatment with Cholesterol-Free Diet in Two Cases, Am. J. Dis. Child. **51**:1372 (June) 1936. Bloom, D.; Kaufman, S. R., and Stevens, R. A.: Hereditary Xanthomatosis, Arch. Dermat. & Syph. **45**:1 (Jan.) 1942. Svendsen, M.: Are Supernormal Cholesterol Values in Serum Caused by a Dominantly Inherited Factor? Report of a Family Investigation of Thirty-Four Individuals, Acta med. Scandinav. **104**:235, 1940.

8. Polano, M. K.: Ueber die Pathogenese der Cholesterosen der Haut, Arch. f. Dermat. u. Syph. **174**:213, 1936.

9. Barker, N. W.: Occlusive Arterial Disease of the Lower Extremities Associated with Lipemia and Xanthoma Tuberosum, Ann. Int. Med. **12**:1891, 1939. Chanutin, A., and Ludewig, S.: Blood Lipid Studies in a Case of Xanthomatosis Associated with Hepatic Damage, J. Lab. & Clin. Med. **22**:903, 1936. Weber, P. F.: Cutaneous Xanthoma and "Xanthomatosis" of Other Parts of the Body—Pituitary Xanthomatosis—"Xanthomyelomata" of the Tendon Sheaths, etc., and "Cholesterin Diathesis," Brit. J. Dermat. **36**:335, 1924. Muller, C.: Xanthomata, Hypercholesterinemia Angina Pectoris, Acta med. Scandinav., 1938, supp. 89, p. 75. Klatskin, G.: Familial Xanthomatosis and Arcus Senilis, Internat. Clin. **3**:13, 1941. Engelberg, H., and Newman, B. Z.: Xanthomatosis: A Cause of Coronary Disease in Young Adults, J. A. M. A. **122**:1167 (Aug. 21) 1943.

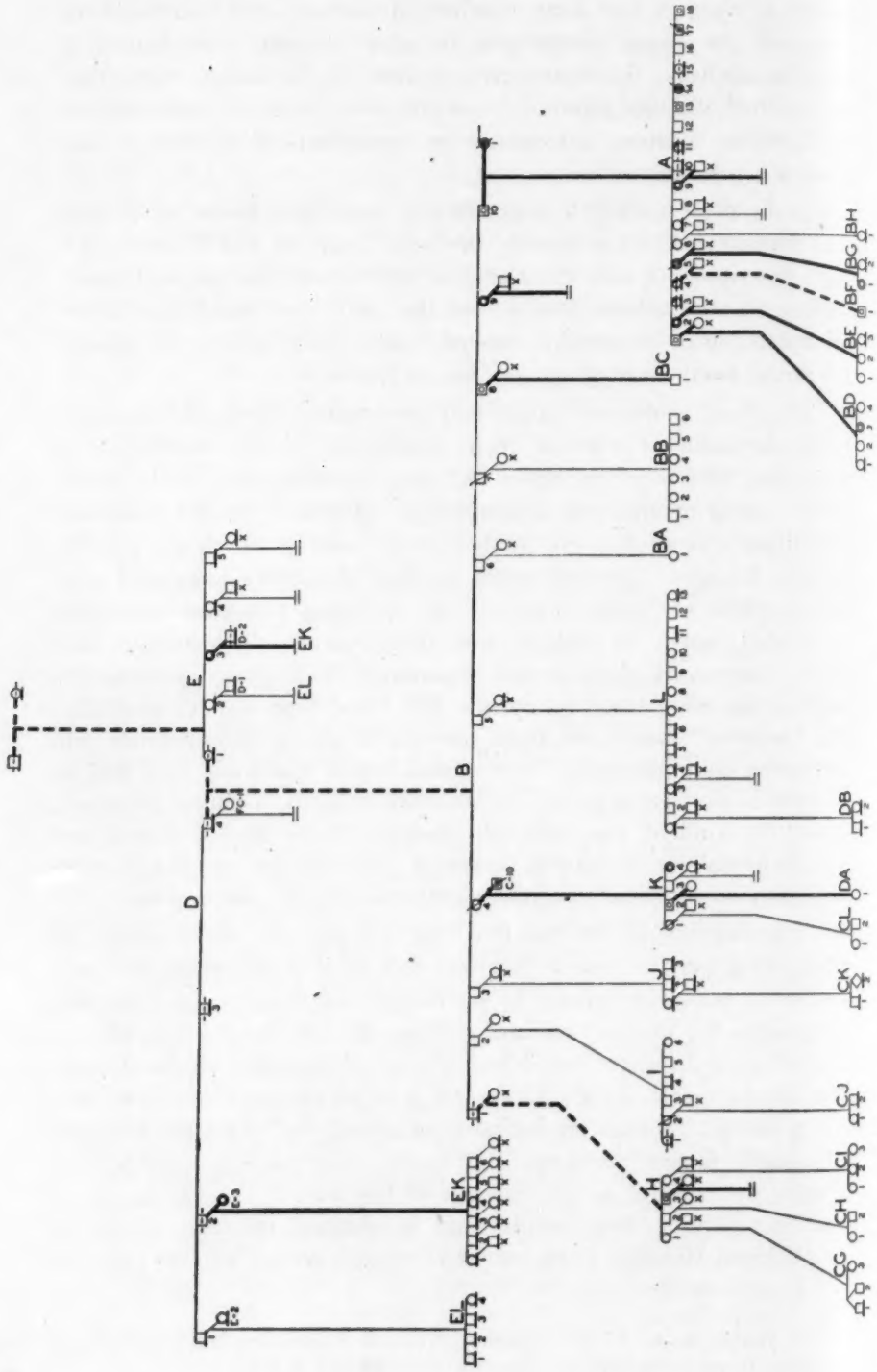
gators to suggest that near relatives of patients with xanthoma be examined for hypercholesteremia or other possible disturbances of lipid metabolism. Unfortunately, in most of the family cases thus far reported adequate physical, blood and other laboratory examinations on direct or collateral antecedents or descendants of affected persons have not been carried out.

In the present study a large kindred, comprising some 270 persons was investigated. In a recently presented study of this kindred we [10] have described not only the historical information and physical observations in all available members of the family but blood lipid determinations and, in certain selected cases, observations on glucose tolerance, basal metabolism and dietary history.

The blood cholesterol values only are presented here and discussed from the point of view of their relationship to the inheritance of xanthoma tuberosum multiplex and their associationship with certain other clinical or anatomic abnormalities. Moreover, several additional hereditary characters were studied in an attempt to detect possible genetic linkages. The heretofore practical difficulties associated with the detection of "genetic carriers" of xanthoma tuberosum multiplex made this search for linkage with these more easily detectable and better understood genes of real importance. This group of characters include the ABO blood group, the MN blood type, the Rh positivity, the "secretor" factor, the taste reaction to phenyl-thiocarbamide and red-green color blindness. It was also hoped that these data will be of interest to those engaged in a statistical analysis of human pedigrees. Since the kindred was primarily studied for its lipid dyscrasia and the abnormalities associated therewith, the records on other factors will provide completely objective estimates of gene frequencies.

The drawing of the pedigree (fig. 1) and the method used for designating persons was as follows: each sibship is lettered and each particular person designated by his or her sibship letter and a number. In general the number indicates position of birth, but because of condensation of the chart this is not true in all instances. Table 1 gives the age in years (as of March 1947) of all persons for whom data are available. Spouses are indicated by a small "x." In a few instances of double family marriages the spouse may have an independent designation, such as in the marriage of B-4 with C-11. Further information regarding these families may be obtained from the University of Michigan Heredity Clinic, where all records on this kindred (number 1064) are on file.

10. Wilkinson, C. F., Jr.; Hand, E. A., and Fliegelman, M. T.: Essential Familial Hypercholesterolemia, Ann. Int. Med. **29**:671, 1948.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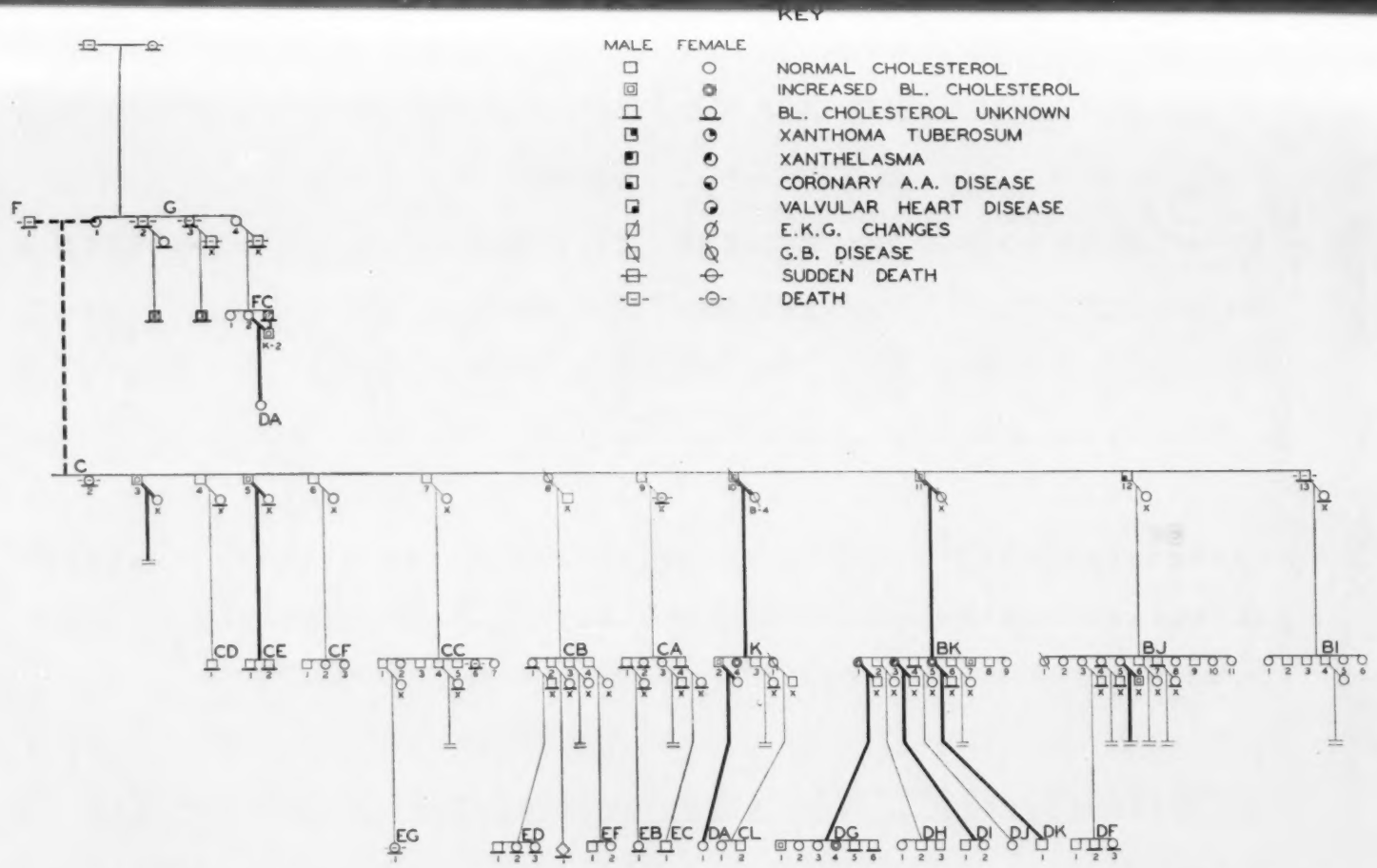

Fig. 1.—Pedigree of kindred exhibiting familial xanthoma tuberosum and essential hypercholesteremia. (The figure is shown in two parts because of the limitation of page dimensions.)

TABLE 1.—*Available Data for Subject in Pedigree (Fig. 1)* *

Subject	Sex	Age, Yr.	Secretor Factor	Taste	Color Vision	Blood Types			Blood Cholesterol, Mg./100 Cc.
A-1	M	30	..	T	..	O	MN	..	350
A-1X	F	26	..	T	Normal	O	MN	..	210
A-2	F	29	..	..	..	O	N	Pos.	433
A-2X	M	32	..	..	..	A_1	N	Pos.	180
A-3	F	25 (d)	..	..	..	..	..	..	...
A-4	F	23 (d)	..	..	..	..	..	..	...
A-4X	M	35	..	..	..	A_1	MN	..	250
A-5	F	23	S	T	Normal	A_2	M	..	335
A-5X	M	27	S	t	..	A_2B	MN	..	208
A-6	F	22	S	T	Normal	A_2	M	..	213
A-6X	M	20-30	..	..	..	..	..	..	262
A-7	F	20	..	..	..	..	..	..	...
A-8	M	19	..	..	..	A_2	M	..	216
A-9	F	25	..	T	Normal	O	MN	..	325
A-9X	M	20-30	..	..	..	..	..	..	262
A-10	M	7 (d)	..	..	..	..	..	..	...
A-11	F	14 (d)	..	..	..	..	..	..	...
A-12	M	14	S	T	Normal	A_2	MN	..	254
A-13	M	12	S	T	(RG-CB)	A_2	M	..	394
A-14	F	11	S	T	(RG-CB)	A_2	M	..	700
A-15	F	5/12 (d)	..	..	..	..	..	..	...
A-16	M	8	S	T	Normal	A_2	MN	..	185
A-17	M	3	S	t ?	..	A_2	M	..	550
A-18	M	1	S	t	..	A_2	MN	..	381
B-1	M	(d)	..	..	..	..	..	..	...
B-1X	F	62	..	..	..	A_1	MN	..	237
B-2	M	53	..	..	..	A_2	M	..	194†
B-2X	F	52	..	..	..	B	MN	..	220
B-3	M	51	..	..	..	..	..	..	187
B-3X	F	49	..	..	..	..	..	..	...
B-4	F	50	S	T	(RG-CB)	A_1B	MN	..	216
B-5	M	47	..	..	..	A_2	N	Neg.	262
B-5X	F	..	..	..	..	..	..	..	...
B-6	M	43	..	..	..	A_1	N	Neg.	217
B-6X	F	36	..	..	..	O	N	Pos.	200
B-7	M	41	..	..	..	A_2	MN	..	183
B-7X	F	35	..	..	..	A_2	M	..	251
B-8	M	38	..	..	..	A_1	MN	..	370
B-8X	F	36	..	..	..	O	M	..	150
B-9	F	46	..	..	..	A_2	N	Pos.	300
B-9X	M	58	..	..	..	..	..	..	...
B-10	M	49	..	T	Normal	A_2	MN	..	446
C-1	F	49	..	T	Normal	O	M	..	288†
C-2	F	41	..	..	..	..	..	..	...
C-3	M	40	..	..	..	B	M	..	420
C-3X	F	42	..	..	..	..	..	..	...
C-4	M	48	..	..	..	A_1	M	..	182
C-4X	F	50	..	..	..	..	..	..	...
C-5	M	44	..	..	..	A_1	M	..	412
C-5X	F	42	..	..	..	A_1	MN	..	...
C-6	M	42	..	..	..	O	M	..	146
C-6X	F	42	..	..	..	A_1	N	..	175
C-7	M	51	..	..	..	O	M	..	153
C-7X	F	49	..	..	..	O	MN	..	225
C-8	F	53	..	..	..	O	MN	..	196
C-8X	M	57	..	..	..	O	MN	..	222
C-9	M	56	..	..	..	O	MN	..	216
C-9X	F	(d)	..	..	..	..	..	..	...
C-10	M	57	S	T	Normal	A_1	M	..	220

TABLE 1.—*Available Data for Subject in Pedigree (Fig. 1)* *—*Continued*

Subject	Sex	Age, Yr.	Secretor Factor	Taste	Color Vision	Blood Types			Blood Cholesterol, Mg./100 Cc.
C-11	M	56	..	T	Normal	O	M	..	350
C-11X	F	50	..	..	..	A_2	N	..	230
C-12	M	59	..	..	..	A_1	M	..	248
C-12X	F	58	..	..	..	O	MN	..	175
C-13	M	(d)	..	..	..	..	..	..	...
C-13X	F	50	..	..	..	..	..	..	...
E-3	F	71	..	..	..	A_1	N	Pos.	315
G-1	F	80	..	T	Normal	O	M	..	161
G-4	F	77	..	..	..	O	MN	..	212
H-1	F	28	..	..	..	A_1	M	..	166
H-1X	M	30	..	..	..	B	MN	..	200
H-2	M	30	..	..	..	A_1B	M	..	186
H-2X	F	28	..	..	..	A_1	M	..	187
H-3	M	29	..	..	..	A_1B	N	Pos.	312
H-3X	F	..	..	..	..	..	..	..	...
H-4	F	31	..	..	..	A_1	MN	..	196
H-4X	M	30	..	..	..	A_1	MN	..	...
I-1	F	4/12 (d)	..	..	..	..	..	..	...
I-2	F	28	..	..	..	A_1B	MN	..	251
I-2X	M	28	..	..	..	A_1	MN	..	220
I-1	M	17	..	..	..	A_1	M	..	215
I-4	M	26	..	..	..	A_1	MN	..	...
I-5	M	25	..	..	..	A_1	MN	..	205
I-6	F	22	..	..	..	A_1B	N	..	125
K-1	F	30	S	t	Normal	A_1B	MN	..	...
K-1X	M	35	..	T	Normal	O	N	..	223
K-2	M	19	S	t	RG-CB	A_2	MN	..	248†
K-3	M	25	S	T	Normal	A_1B	N	..	140
K-3X	F	23	S	T	Normal	B	N	..	...‡
K-4	F	20	S	T	Normal	A_1B	MN	..	283
L-2	M	22	..	..	..	A_2	N	Neg.	237
L-7	F	10	..	..	..	O	N	Neg.	158
L-8	F	7	..	..	..	O	N	Pos.	166
L-9	M	7	..	..	..	A_2	N	Pos.	160
L-10	F	2	..	..	..	O	N	Pos.	187
L-12	M	3	..	..	..	A_1B	N	Pos.	200
L-13	F	13	..	..	..	A_1	N	Neg.	...
BA-1	F	17	..	..	..	A_1	N	Neg.	210
BB-1	M	14	..	..	..	A_2	MN	..	215
BB-2	F	13	..	..	..	A_2	MN	..	251
BB-3	F	9	..	..	..	O	MN	..	251
BB-4	F	7	..	..	..	A_2	M	..	220
BB-5	M	5	..	..	..	A_2	MN	..	237
BB-6	M	4	..	..	..	A_2	MN	..	...
BC-1	M	10	..	..	..	O	MN	..	271
BD-2	F	6	..	T	Normal	..	..	..	190
BD-3	F	4	..	t	..	O	M	..	425
BD-4	F	3	..	t	..	O	M	..	187
BE-1	F	7	..	..	..	A_2	N	Pos.	187
BE-2	F	4	..	..	..	A_1	N	Pos.	237
BE-3	F	1/12	..	..	..	..	..	..	...
BF-1	M	4	..	..	..	O	M	..	415
BG-1	F	4	S	t	..	A_1	M	..	316
BG-2	F	1	..	..	..	..	..	..	...
BI-1	F	32	..	..	..	O	MN	..	147
BI-2	M	28	..	..	..	A_1	MN	..	205
BI-3	M	25	..	..	..	O	MN	..	135
BI-4	M	29	..	..	..	O	MN	..	152
BI-4X	F	20-30	..	..	..	..	..	..	187

TABLE 1.—*Available Data for Subject in Pedigree (Fig. 1)* *—*Continued*

Subject	Sex	Age, Yr.	Secretor Factor	Taste	Color Vision	Blood Types			Blood Cholesterol, Mg./100 Cc.
BI-5	F	19	..	..	..	O	MN	..	135
BI-6	F	23	..	..	..	A_1	M	..	275
BJ-1	F	34	..	..	..	O	M	..	169†
BJ-2	F	32	..	..	..	A_1B	M	..	141†
BJ-3	F	31	..	t	Normal	A_1B	MN	..	200
BJ-3X	M	33	..	..	..	O	N	..	...
BJ-4	F	29	..	..	..	B	MN	..	...
BJ-4X	M	30	..	..	..	O	MN	..	...
BJ-5	F	27	..	..	..	A_1	MN	..	225
BJ-5X	M	29	..	..	..	O	M	..	286
BJ-6	M	25	..	..	..	A_1	MN	..	133†
BJ-6X	F	20	..	..	..	A_2B	M	..	208
BJ-7	M	24	..	..	..	..	..	..	...
BJ-7X	F	18	..	..	..	..	..	..	...
BJ-8	F	23	..	..	..	O	M	..	151†
BJ-9	M	21	..	..	..	A_1	MN	..	188
BJ-10	F	18	..	..	..	O	MN	..	119†
BJ-11	F	16	..	..	..	O	MN	..	116†
BK-1	F	34	S	T	Normal	A_1	MN	..	430
BK-1X	M	34	..	T	RG-CB	A_1B	N	..	163
BK-2	M	32	S	T	Normal	A_1	MN	..	210
BK-2X	F	27	S	..	..	A_1	MN	..	152
BK-3	F	30	S	T	Normal	A_1	MN	..	433
BK-3X	M	32	..	..	..	..	..	..	175
BK-4	M	28	..	T	Normal	O	MN	..	...
BK-4X	F	22	..	T	Normal	O	MN	..	227
BK-5	F	25	S	T	Normal	A_1	MN	..	333
BK-6	M	23	..	T	Normal	O	MN	..	170
BK-6X	F	21	..	T	Normal	..	..	..	204
BK-7	M	22	S	T	Normal	A_2	MN	..	337
BK-8	M	20	S	T	Normal	A_1	MN	..	205
BK-9	F	19	S	T	Normal	A_1	MN	..	188
CA-1	M	30	..	..	..	..	..	..	...
CA-1X	F	26	..	..	..	O	MN	..	...
CA-2	F	24	..	..	..	..	..	..	...
CA-3	F	21	..	..	..	O	MN	..	140
CA-4	M	28	..	..	..	O	MN	..	...
CA-4X	F	..	..	..	..	O	M	..	...
CB-1	F	30	..	..	..	..	..	..	...
CB-1X	M	33	..	..	..	..	..	..	...
CB-2	M	27	..	..	..	O	M	..	215
CB-2X	F	23	..	..	..	..	..	..	...
CB-3	M	26	..	..	..	O	M	..	210
CB-3X	F	21	..	..	..	..	..	..	200
CB-4	M	29	..	..	..	O	M	..	193†
CB-4X	F	23	..	..	..	O	MN	..	175
CC-1	M	29	..	..	..	O	MN	..	175
CC-1X	F	25	..	..	..	B	N	..	155
CC-2	F	26	..	..	..	O	MN	..	165
CC-3	M	24	..	..	..	O	M	..	169†
CC-4	M	22	..	..	..	B	MN	..	183
CC-4X	F	20-30	..	..	..	O	MN	..	...
CC-5	F	19	..	..	..	O	MN	..	167
CC-6	F	3 (d)	..	..	..	..	..	..	...
CC-7	F	10	..	..	..	O	MN	..	170
CE-1	M	8	..	..	..	A_1	MN	..	...
CE-2	M	1	..	..	..	..	..	..	...
CF-1	M	12	..	..	..	O	MN	..	182
CF-2	F	15	..	..	..	O	MN	..	250

TABLE 1.—*Available Data for Subject in Pedigree (Fig. 1)* *—*Continued*

Subject	Sex	Age, Yr.	Secretor Factor	Taste	Color Vision	Blood Types			Blood Cholesterol, Mg./100 Cc.
CF-3	F	3	..	..	..	A_1	MN	..	175
CG-1	M	3	..	..	..	O	M	..	...
CG-2	M	3	..	..	..	O	MN	..	170
CG-3	F	5	..	..	..	..	..	..	170
CH-1	F	6	..	..	..	A_1	MN	..	200
CH-2	M	2	..	..	..	A_1B	MN	..	187
CI-1	F	5	..	..	..	O	MN	..	200
CI-2	F	1	..	..	..	A_1	MN	..	...
CI-3	F	8	..	..	..	O	MN	..	158
CJ-1	F	6	..	..	..	A_1	MN	..	...
CJ-2	M	1/12	..	..	..	..	..	..	...
CL-1	F	11	S	T	Normal	A_1	MN	..	187
CL-2	M	7	S	T	Normal	A_1	M	..	250
DA-1	F	2	S	..	..	A_2	MN	..	175
DF-1	M	5	..	..	..	A_1	N	..	183
DF-2	M	4	..	..	..	A_1	MN	..	...
DF-3	F	3	..	..	..	O	MN	..	...
DG-1	M	9	S	T	Normal	A_1	MN	..	406
DG-2	F	7	S	T	Normal	A_2B	M	..	196
DG-3	F	6	S	T	Normal	A_1	MN	..	196
DG-4	F	5	s	T	Normal	A_1B	MN	..	341
DG-5	M	3	..	..	..	A_2B	MN	..	...
DG-6	M	1	..	..	..	..	..	..	...
DH-1	F	7	..	..	..	A_1	MN	..	153
DH-2	M	6	..	T	Normal	A_1	N	..	160
DH-3	M	3	S	T	..	A_1	MN	..	160
DI-1	M	2	S	T	..	A_2	MN	..	152
DI-2	F	5	..	..	..	O	M	..	205
DJ-1	F	3	..	t	..	O	MN	..	142†
DK-1	M	3	..	T	..	A_1	M	..	165
EB-1	F	3	..	..	..	A_1	M	..	...
EC-1	M	3	..	..	..	B	MN	..	...
EF-1	M	3	..	..	..	..	..	..	208
EF-3	F	6	..	..	..	O	MN	..	153
EG-1	F	2 (d)	..	..	..	O	N	..	...
FC-1	F	57	..	..	..	A_1	M	..	237
FC-2	F	48	..	T	Normal	O	MN	..	196

* S is secretor, s is nonsecretor, T is taster, t is nontaster, RG-CB is red-green color blindness, (RG-CB) means retest was indicated, because of possible inability to read numbers, low mentality or inattention, and (d) means the subject died at the stated age prior to March 1947 or during the course of study.

† Schoenheimer-Sperry method.

‡ The subject was pregnant when the study was made.

METHODS OF STUDY

1. *Blood Lipid Tests.*—A modified Bloor [11] method for determining blood cholesterols was used in the initial survey because of the large number of persons involved. The method was later changed to the more accurate and time-consuming Schoenheimer-Sperry [12] technic,

11. Todd, J. C., and Sanford, A. H.: Clinical Diagnosis, ed. 10, Philadelphia, W. B. Saunders Company, 1943, p. 380.

12. Schoenheimer, R., and Sperry, W. M.: Micromethod for Determining Free and Combined Cholesterol, J. Biol. Chem. **106**:745, 1934.

when certain metabolic studies, which are still being carried out, were started. Consequently, the few values determined by the latter method are designated in table 1 by a dagger.

Figure 2 shows the frequency distribution of blood cholesterol levels. Rather than presenting the normal or bell-shaped curve the curve appears to be bimodal, as might be expected if the group were comprised of two genetically different types. The minimal point between the two groups is in the neighborhood of 280 mg. per hundred cubic centimeters, the value adopted as our criterion for hypercholesteremia. The appropriateness of this level is perhaps further substantiated by the fact that the 30 relatives classified as hypercholesteremic show levels in agreement with the predicted genetic pattern of transmission, as will be discussed later.

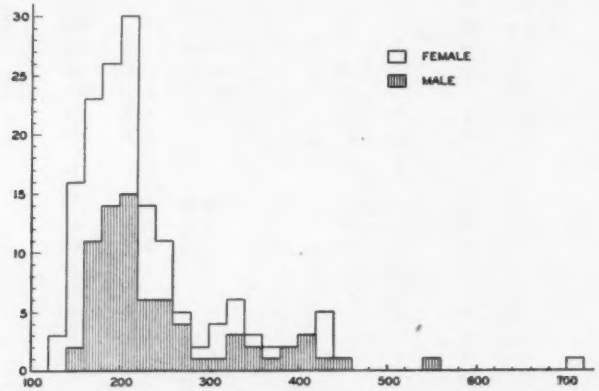

Fig. 2.—Frequency distribution curve of blood cholesterol levels of 159 members of kindred. The vertical column of figures shows the number of subjects and the horizontal line of figures shows the blood cholesterol values in milligrams per hundred cubic centimeters.

We considered 210 mg. per hundred cubic centimeters by the Schoenheimer-Sperry method as our hypercholesteremic level, although they have all been expressed in Bloor method figures in figure 2.

A further point in substantiation of these values lies in the consideration of the 3 persons called normocholesteremic by us (B-5, BI-6, BC-1) whose blood cholesterol values exceeded 260 mg. per hundred cubic centimeters by the Bloor or 200 mg. per hundred cubic centimeters by the Schoenheimer-Sperry technic. B-5 is the father of many children. The 5 seen by us all had definitely normal blood cholesterol levels. BI-6 is 1 of 6 children, the 5 others having normal blood cholesterol levels. BC-1 is the only child of a hypercholesteremic father and a normocholesteremic mother, and so his chances of being one or the other are about equal.

2. ABO, MN and Rh Blood Classification.—A specimen of a few drops of the venous blood drawn for the lipid studies was refrigerated as saline suspensions and tested within forty-eight hours of collection. The tests for the presence of agglutinogens A_1, A_2, B, M, N and Rh were made with standard testing serums and 2 per cent cell suspensions. In each series of tests control bloods of the ABO, MN and Rh classifications were used.

3. Secretor Test.—It has been known for many years that the saliva (as well as other body fluids) of certain persons of groups A, B and AB contained the corresponding antigens in concentrations that are higher than the red blood cells, while the saliva of other persons may contain virtually none of these antigens. While the mechanism of this condition is obscure, it is inherited as a single gene difference, the secretor condition being dominant to the nonsecretor. Furthermore, the difference, as shown by Schiff and Sasaki,[13] was also found in group O persons. The method of performing this test has been previously described by Cotterman and Falls.[14]

4. Taste Test.—While the determination of "tasters" and "nontasters" of phenyl-thiocarbamide is undoubtedly best done with serial dilutions of a saturated solution thereof, in this study small quantities of the powdered crystals were placed on the tongue. Subjects were asked to describe the taste. There were no control test substances employed, and in some instances there were children tested who were perhaps too young for reliable diagnosis. Moreover, it was usually necessary to test a subject in circumstances which allowed that person to learn the reactions of those about him who were being tested at the same time. Nevertheless, the results appear to be sufficiently accurate for linkage detection.

5. Color Blindness.—The subjects were tested for color blindness with the pseudoisochromatic charts of Ishihara and Stilling.

Table 1 presents the data on this kindred that is presently available.

COMMENT

The original patients for our pedigree are the sister and brother A-14 and A-17, both suffering from xanthoma tuberosum multiplex. In a preliminary visit to their home it was not only suggested to us that there was a definite pattern of inheritance of the abnormality, but we discovered that 2 older sisters (A-3, A-4), now no longer

13. Schiff, F., and Sasaki, H.: Ueber die Vererbung des serologischen Ausscheidungstypus, Ztschr. f. Immunitätsforsch. u. exper. Therap. **77**:129, 1932.

14. Cotterman, C. W., and Falls, H. F.: Genetic Studies on Ectopia Lentis, Ann. Eugenics **12**:158, 1944.

living, had also suffered from this same syndrome and had been studied by Curtis, Wile, Duemling and Eckstein [15] at the University of Michigan. Their hospital records were available to us, and, while blood cholesterol values had not been reported, the photographs and other clinical and pathologic data make certain the diagnosis of xanthoma tuberosum multiplex. Another sister (A-11), now dead, was reliably reported to have had xanthoma tuberosum lesions.

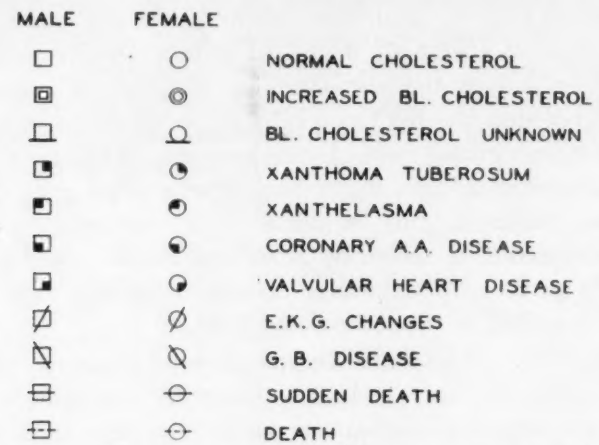

Fig. 3.—Enlarged reproduction of key taken from figure 1.

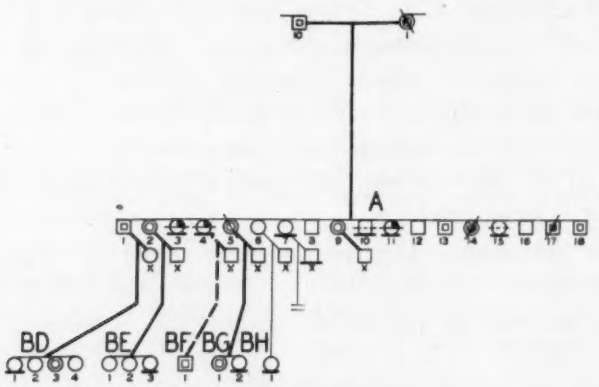

Fig. 4.—Sibships A and BF.

This kindred contains four distinctly different types of matings: a hypercholesteremic person with a hypercholesteremic one, a nor-

15. (*a*) Curtis, A. C.; Wile, U. J., and Eckstein, H. C.: The Involution of Cutaneous Xanthomata Caused by Diets Low in Calories, J. Clin. Investigation **7**:249, 1929. (*b*) Wile, U. J., and Duemling, W. W.: Familial Xanthoma, Arch. Dermat. & Syph. **21**:642 (April) 1930. (*c*) Wile, U. J.; Eckstein, H. C., and Curtis, A. C.: Lipid Studies in Xanthoma: Further Contribution, ibid. **20**:489 (March) 1929.

mal person with one suffering from xanthoma tuberosum multiplex, a normal person with a normal one and a normal person with a hypercholesteremic one. The observations in offspring of these matings have caused us to consider xanthoma tuberosum multiplex the homozygous abnormal state, the heterozygous state producing hypercholesteremia alone.

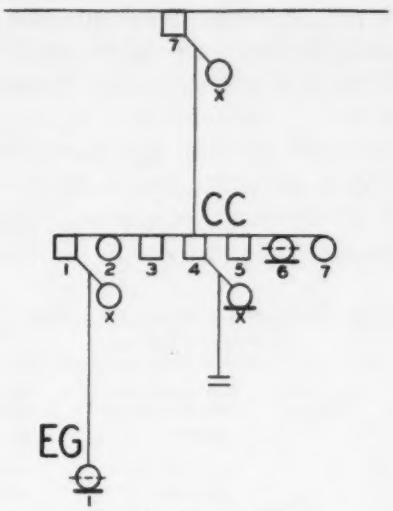

Fig. 5.—Sibship CC.

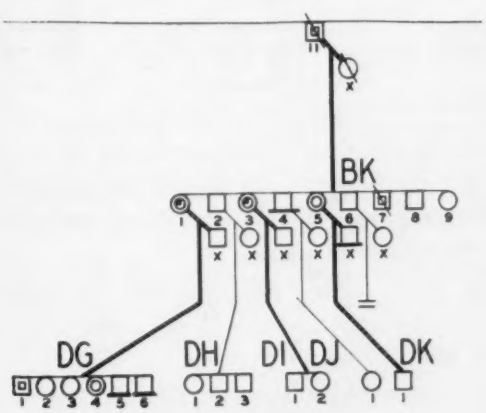

Fig. 6.—Sibship BK.

The various matings of these persons with their resultant mendelian ratios are well illustrated. The symbols for the various known abnormalities in these persons, enlarged from figure 1, is shown in figure 3. Sibship A, (fig. 4) for example, is the result of the mating of two heterozygotes (C-1 and B-10) who had increased blood cholesterol values. The heavy black line connecting and descending vertically

from them denotes the transmission of this abnormal trait through this mating. The expected ratio of 1 homozygous abnormal person, 2 heterozygous persons and 1 homozygous normal person is approximated. Actually, of the 18 children in this sibship 5 had xanthoma tuberosum and/or tendinosum (A-3, A-4, A-11, A-14, A-17), 6 had elevated blood cholesterol levels without cutaneous lesions (A-1, A-2, A-5, A-9, A-13, A-18) and 4 had normal blood cholesterol values (A-6, A-8, A-12, A-16). Three are reported not to have had cutaneous lesions (A-7, A-10, A-15), but their cholesterol levels are not known.

In the union of A-4, who had xanthoma tuberosum, and A-4_x (fig. 4), whose blood cholesterol was normal, the only possible type of offspring must be the hypercholesteremic heterozygote, if our thesis is correct. The only child (BF-1) showed the expected increased

TABLE 2.—*Numbers of Affected and Normal Children Among Offspring of Various Matings*

Matings	Number of Matings	Elevated Blood Cholesterol Level	Normal Blood Cholesterol Level	Unexamined
Heterozygote X Heterozygote	1	Observed— 8 Expected— 9	Observed— 4 Expected— 3	6
Heterozygote X Normal	9	Observed—11 Expected—12	Observed—13 Expected—12	5
Normal X Normal	11	Observed— 0 Expected— 0	Observed—41 Expected—41	7
Homozygous abnormal X Normal	1	Observed— 1 Expected— 1	Observed— 0 Expected— 0	0

blood cholesterol value but no cutaneous lesions at the age of 3. (The heavy broken line indicates the anticipated transmission of the abnormal trait since this person (A-4) had been studied by Curtis and his co-workers [15a] and not by us.)

The elevated blood cholesterol levels are transmitted to the succeeding generation by other members of sibship A, as indicated by the heavy black lines shown in figure 4.

Normal offspring would, of course, be expected to result from the mating of 2 normal parents (C-7 and C-7_x). Sibship CC (fig. 5) illustrates this. It is comprised of 6 living persons who were normal on physical examination, all of whom had normal blood cholesterol levels, and 1 dead (CC-6), whose blood cholesterol level was not determined.

The progeny resulting from the union of a normal person (C-11_x) with a heterozygote (C-11) are found in the expected ratio of 1 normal person to 1 heterozygote, as can be seen in sibship BK (fig. 6).

Here none of the 8 children examined had cutaneous lesions, but 4 (BK-2, BK-6, BK-8, BK-9) had normal and four (BK-1, BK-3, BK-5, BK-7) had elevated blood cholesterol levels. One (BK-4) was not seen by us.

Again, where there are enough offspring in the next generation of this family line, the hypercholesteremia is transmitted (as indicated by the heavy black lines) in the usual ratio.

More detailed reference to the pedigree will reveal other illustrations of some of these types of matings, and table 2 shows the total observed and expected numbers of affected and normal children among the offspring of the various types of matings when both parents had been examined and their blood cholesterol levels determined. There were two possible matings (homozygous abnormal with homozygous abnormal and homozygous abnormal with heterozygote) that were not

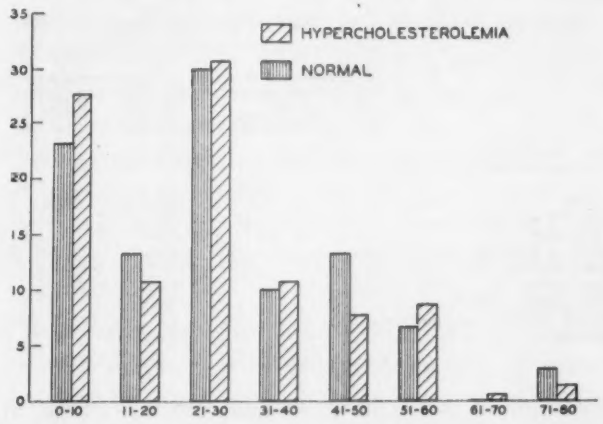

Fig. 7.—Percentage distribution by age of 30 hypercholesteremic and 129 normocholesteremic persons. The horizontal row of figures shows the age in years, and the vertical column of figures shows the percentage of the group.

found in this kindred. It should also be noted that both the homozygous abnormal and heterozygous state of this condition may be detected very early in life by appropriate blood and physical examinations. Moreover, even at an early age the homozygous person with two abnormal genes has a higher blood cholesterol level (over 500 mg. per hundred cubic centimeters in this kindred), while the heterozygous person tends to have a more moderate elevation (283 to 446 mg. per hundred cubic centimeters).

While the kindred studied is composed of some 270 persons, only 159 will be included in our statistical studies because only this number was studied sufficiently to rule out other common causes of hypercholesteremia (nephrotic syndrome, diabetes, hypothyroidism, pregnancy and hepatic disease) and included all cooperative and available

members of the kindred. Of these 159, 30 had elevated blood cholesterol levels and 129 had normal levels.

The age incidence of the normal and abnormal blood cholesterol level groups is shown in figure 7.

Many investigators [9] have associated certain clinical and/or anatomic abnormalities with xanthomatous deposits in the skin, and the relative frequency of these complications in this kindred is shown in table 3.

Two of the hypercholesteremic groups studied by us had xanthoma tuberosum and/or tendinosum, while 3 others, as discussed elsewhere, also showed xanthomatous lesions of the skin.

Xanthelasma was found in 3 subjects in the group with elevated cholesterol levels and in 1 subject in the group with normal blood cholesterol levels.

TABLE 3.—*Relative Frequency of Clinical and/or Anatomic Abnormalities*

	Hypercholesteremia		Normocholesteremia	
	Number of Subjects (Total 30)	Percentage	Number of Subjects (Total 129)	Percentage
Xanthoma tuberosum / Xanthoma tendonosa	2	6.6	0	0.0
Xanthelasma	3	10.0	1	0.8
Arcus juvenilis/senilis	0	0.0	1	0.8
Angina pectoris	1	3.3	1	0.8
Xanthomatous valvular heart disease	2	6.6	0	0.0
Gallbladder disease				
Clinical story	5	17.0	7	5.4
Roentgenogram taken	5	0.0	4	0.0
Roentgen observation positive	2	6.6	1	0.8
Hepatomegaly	5	17.0	3	2.3

Only 1 case of arcus senilis was found, and it occurred in a subject with a normal cholesterol level. However, it should be emphasized that no slit lamp examinations were performed.

No cases of myocardial infarction were found by us, but, since A-3, A-4 and A-11 all died suddenly and since they all had xanthoma tuberosum, it may well be suspected.

Both A-14 and A-17 had valvular heart disease, and, since there was no history of chorea, scarlet fever, diphtheria or rheumatic fever, it seems justifiable to assume that these valvular defects were due to xanthomatous deposits. A detailed analysis of the electrocardiographic observations and a cardiac evaluation of this kindred will be presented elsewhere.

A clinical history of gallbladder disease was found for 5 of the hypercholesteremic group and 7 of the normocholesteremic group, while 5 of the former group showed hepatomegaly and only 3 of the latter group demonstrated this abnormality.

No cases of biliary cirrhosis were found.

In the group of 30 persons with elevated cholesterol levels there were exactly 15 of each sex.

A review of the genetic factors studied reveals that the ABO, MN and Rh blood groupings were inherited in the usual fashion. Two discrepancies were found. Both BJ-2 and BJ-3 were recorded as type A_1B persons and were the offspring of C-12, who was type A, and C-12_X, who was type O. Progeny of such a mating could not possibly be type A_1B, but since, from the blood cholesterol point of view, C-12, C-12_X and all their offspring had normal values this observation did not invalidate our primary thesis.

Both the secretor factor and the ability to taste phenyl-thiocarbamide were found to be inherited in this kindred in the usual fashion.

Red-green color blindness of the deuteranopia type was found in one sibship (K) of those tested. This anomaly could not be traced further by either testing or hearsay evidence.

No complete linkage was found between blood cholesterol levels and any of the genetic factors studied, but a final analysis of them has not been made.

In the light of these data we feel that the metabolic disorder manifested by an increased blood cholesterol value, designated and discussed elsewhere by us as "essential familial hypercholesterolemia," [10] is transmitted as if due to a single abnormal gene which is incompletely dominant to its normal allele.

The three possible combinations of these genes comprise: (*a*) the homozygous normal person with two normal genes, (*b*) the heterozygote who has one abnormal gene and hypercholesteremia and (*c*) the homozygous abnormal person with two pathologic genes and showing not only hypercholesteremia but xanthoma tuberosum multiplex as well and, in many instances, cardiovascular system damage and other abnormalities.

This mode of inheritance, when the heterozygous person with one abnormal gene is distinguishable from the homozygote affected with two abnormal genes, is called incomplete or intermediate dominance. Obviously, the homozygote affected person will transmit an abnormal gene to all of his or her offspring, but the ability to recognize the heterozygous state is of the greatest practical importance, for it is these persons who are the genetic carriers of the abnormal gene. (In a broad sense a "genetic carrier" is one who may transmit an inherited disease or produce more carriers in progeny without actually showing the commonly accepted observations of the full blown disease himself.[16])

16. Neel, J. V.: The Clinical Detection of the Genetic Carriers of Inherited Disease, Medicine **26**:115, 1947.

The discovery of this method for the detection of the heterozygous carriers is a major step forward in the early diagnosis of this inherited disease. It is certainly a prerequisite for its genetic control. That such control is indicated is indisputable.

SUMMARY AND CONCLUSIONS

Essential familial hypercholesteremia is transmitted as an incomplete dominant trait. Xanthoma tuberosum multiplex represents the homozygous state for an inherited factor which when heterozygous produces only hypercholesteremia. The upper limit of normality for blood cholesterol levels has been established statistically and genetically. Neither sex nor age influence the occurrence of hypercholesteremia. The greater incidence of certain pathologic conditions in the abnormal group as compared to the normal group is illustrated. It is now possible to predict the matings which may be expected to produce a person with xanthoma tuberosum multiplex: the matings of 2 homozygous abnormal persons, or of a homozygous abnormal with a heterozygote or that of 2 heterozygotes.

ABSTRACT OF DISCUSSION

DR. HAMILTON MONTGOMERY, Rochester, Minn.: Dr. Fliegelman and his associates have done an excellent job on the genetics of xanthoma. The paper is concise and should be read word for word and then reread. I am glad to see this paper come from Ann Arbor because it amplifies the facts on 2 cases of juvenile xanthoma in the same family reported by Drs. Wile, Curtis and Eckstein in THE ARCHIVES in 1929. The studies of Dr. Fliegelman and his associates confirm and surpass the studies of genetics reported in an excellent paper some years ago by Müller (*Arch. Int. Med.* **64**:675-700 [Oct.] 1939). I wish to emphasize that practically all patients with xanthoma tuberosum have hyperlipemia and hypercholesteremia and that in 40 per cent or more of the cases there is associated cardiovascular disease in the form of angina pectoris and coronary sclerosis or intermittent claudication and arteriosclerosis obliterans. I would like to ask Dr. Fliegelman why children more frequently have lesions of the mitral valve than elsewhere and why in adults, when the heart is affected, the coronary arteries are involved. It is important to recognize that xanthoma tuberosum often occurs as a familial disease and that angina pectoris occurs at an earlier age in adults with xanthoma tuberosum, usually in the early forties, than in the general adult population, in which the highest incidence is in the fifties and sixties. In a given family one member may have hypercholesteremia without evidence of coronary disease for a period of many years, another may have xanthoma tuberosum, hypercholesteremia and coronary disease and in others cutaneous manifestations may be limited to small xanthelasma of the eyelids, yet with systemic xanthomatosis. In about 15 per cent of the cases of xanthoma tuberosum, there is evidence of hepatic involvement, usually in the form of xanthomatous biliary cirrhosis. If patients with xanthoma tuberosum associated with cardiovascular disease are put on a rigid, animal fat-free diet plus a supplement of necessary vitamins, the early cutaneous lesions will involute, but more important the blood plasma lipids can often be returned to normal and further damage to the cardiovascular system can be minimized. I know of a former student who

has outlived by at least ten years his anticipated life expectancy by adhering to such a diet. In xanthoma limited to the eyelids, about 50 per cent of the patients have hypercholesteremia, and of the 50 per cent about half have evidence of cardiovascular disease; hence the presence even of xanthelasma calls for determination of blood plasma lipids. The dermatologist, therefore, can be of assistance to the internist, because in xanthoma tuberosum and xanthelasma he can anticipate that certain patients will have coronary disease because of the cutaneous manifestations and because of the hypercholesteremia and hyperlipemia.

DR. JOHN GARB, New York: Dr. Fliegelman and his associates confirm the theory recognized by most investigators that hypercholesteremia is the basic underlying disturbance in the inheritance of xanthoma tuberosum. As far as the large family which they studied is concerned they have proved that hypercholesteremia with or without xanthelasma is due to one defective gene, present in a heterozygotic person, while a homozygote manifests not only hypercholesteremia but also xanthomatosis of the skin with or without cardiovascular involvement. This genetic behavior of the syndrome would be comparable to that of brachydactyly which is believed to reveal itself in the homozygotic state in a severer form than in the heterozygotic state. Although the authors' contention is borne out in their case pedigrees, studies in this one family may not be sufficient to prove the general validity of this mode of transmission in all cases of xanthoma tuberosum. Additional families and more cases would be required to consider their concept as universally applicable. Dr. David Bloom and his associates of New York Skin and Cancer Unit conceived the hypothesis that hypercholesteremia, cutaneous xanthomatosis and cardiovascular involvement with or without sudden death, alone or combined, constitute a syndrome which may be manifested fully or partially—comparable to the syndrome of adenoma sebaceum and tuberous sclerosis. They stated the belief that even the expression of the full syndrome does not require a homozygotic person and the presence of only one defective gene is sufficient. According to this opinion xanthomatosis as a dominant disease may manifest itself in the heterozygotic state as hypercholesteremia alone or associated with xanthoma tuberosum with or without cardiovascular disease, or as hypercholesteremia with cardiovascular complication without cutaneous xanthomatosis.

The general validity of the concept of Dr. Fliegelman and his associates that the homozygote has severer clinical manifestations than the heterozygote is contradicted in the literature by studies of at least one family. In this unusual family reported by Bloom, Kaufman and Stevens (Hereditary Xanthomatosis, ARCH. DERMAT. & SYPH. **45**:1 [Jan.] 1942), the 5 siblings, even though they had the full syndrome of hypercholesteremia, xanthoma tuberosum and cardiovascular disease, with sudden death in 4, could not have been homozygotes because the mother was normal and the father had hypercholesteremia alone and, according to Dr. Fliegelman, could be considered only a heterozygote.

I agree with Dr. Fliegelman regarding the importance of blood cholesterol studies in relation to cases of xanthoma tuberosum. It is fortunate that in this syndrome the elevated blood cholesterol level is a warning of the disease. Dietary measures of low cholesterol and low fat with perhaps administration of lipocaic (pancreatic extract) or a lipotropic substance, such as lecithin, and routine examinations carried out regularly and periodically for life may possibly prevent xanthomatous lesions with serious complications, especially in the cardiovascular apparatus. May I suggest that a routine blood cholesterol test, like a Wassermann test, would be valuable in clinics and in private practice? It may reveal many cases in which there are elevated blood cholesterol levels and other stigmas of disturbed

lipid metabolism. Too little attention has been paid to this important branch of science, which, if applied to research, would aid in solving many obscure problems and might reveal the basis of metabolic and other disorders affecting the heart, vascular tree, viscera and skin. Drs. Fliegelman, Wilkinson and Hand must be congratulated for their vast and painstaking study of such a vital inherited disease and for the stimulation that it ought to give generally and particularly to the investigation of genetics in the field of dermatology.

Dr. David Adlersberg, New York: I wish to speak from the point of view of the internist interested in this syndrome because of the well established association of xanthomatosis, coronary artery disease and hypercholesteremia. A study of families with xanthomatosis by Drs. Boas, Parets and myself revealed many interesting facts. First, this disorder is not so rare as we originally thought. In the course of the first few months, we had examined and reported on 55 members belonging to seven families, as well as 9 additional patients whose families were not available for study. The study being at present prepared for publication includes thirty-two families and reveals that only a small group of the members manifest the full syndrome, namely, xanthoma tuberosum or tendinosum, xanthelasma, arcus juvenilis, atherosclerosis of the coronary arteries and hypercholesteremia. In the other subjects, the lesions may be found in various combinations. Some of the subjects present only the cutaneous lesions and hypercholesteremia and others only coronary artery disease with or without xanthomatosis and with or without arcus juvenilis. The most constant feature is the elevation of the blood cholesterol level, which may be found, not infrequently, even among children of these families. We consider, at present, only levels above 300 mg. per hundred cubic centimeters as abnormal. The practical importance of this disorder may be illustrated by the following case. A woman of 43 was admitted to the hospital with coronary thrombosis. She had xanthelasma of the eyelids and a blood cholesterol level of 525 mg. per hundred cubic centimeters. She survived the attack but died, at home, a few months later from another coronary occlusion. Two brothers and one sister of the patient had blood cholesterol levels ranging from 450 to 560 mg. Two other brothers had died at the ages of 31 and 37 of coronary artery disease. A complete autopsy report of the younger brother was available and revealed severe atherosclerosis of the coronary arteries; his blood cholesterol was not studied, and it was not known, at that time, that he belonged to a hypercholesteremic family. It was only fifteen years later, when his sister was observed at the hospital and the whole family studied, that the true nature of the disorder became apparent. Studies of young persons with coronary artery disease has unmasked many similar instances of hereditary hypercholesteremia.

We had the impression that families with xanthoma represent only the extremes of disturbed lipid metabolism and that many persons with seemingly uncomplicated coronary artery disease may fall into a similar pattern. A study of 122 consecutive patients with proved coronary artery disease below the age of 50 confirmed this impression. In 58 per cent of these patients the serum cholesterol level was elevated over 300 mg. per hundred cubic centimeters. Arcus juvenilis was exhibited by 22, xanthelasma by 12 and xanthoma by 3. In one third of fifty families of this group was hypercholesteremia found in all or most of the siblings, and, in addition, in nine more families one half of the siblings showed hypercholesteremia.

As far as therapy is concerned, a cholesterol-free diet with the addition of lecithin deserves a trial. The results are not too satisfactory, although some persons show a striking drop in the serum cholesterol level. The role of dietary

cholesterol in hypercholesteremia is not established. We definitely know that cholesterol can be synthesized in the body, e. g., from acetic acid. Since hypercholesteremia reflects a metabolic disturbance, efforts are justified to modify its influence on the vascular system much as one attempts to obviate the complications of diabetes by diet and insulin therapy. A pharmacologic counterpart to insulin for the treatment of hypercholesteremia is not beyond the realm of possibility but is not available at present.

Dr. David Kahn, Lansing, Mich.: In predicting the occurrence of xanthoma tuberosum from the blood cholesterol value, a word of caution may be in order. Several years ago, in studying a group of psoriatic patients, my associates and I noted great variations in blood cholesterol values, when determined at weekly or biweekly intervals over a period, in some cases, of a year or longer. It is therefore advisable that one do a number of cholesterol determinations in each patient before coming to a final decision.

Dr. Charles F. Wilkinson, Ann Arbor, Mich.: I stated in San Francisco, at the American College of Physicians, several weeks ago, that we also found coronary lesions in the younger subjects. One girl was reported who had had angina pectoris since the age of 9. In answer to Dr. Garb's justifiable criticism that only one family had been reported, I may add that three additional families, in which xanthoma tuberosum was present, have also been studied in detail. These studies will be the subject of two additional papers, one by Dr. Hand and myself and one by Colonel Fancher and myself. In addition, six other families with essential familial hypercholesteremia, but in which xanthoma tuberosum did not exist, have been studied in great detail. None of these patients have xanthoma as a result of the marriage when one parent had normocholesteremia.

With regard to the paper referred to by Bloom and his associates, the cholesterol was reported to be normal in the mother. However, no values were given. One thing that we could not explain is that the mother was designated with a question mark in the original paper. It would seem there was only one determination of the blood cholesterol, which was not reported, and, for one reason or another, the results were questionable. It was also reported that half of the siblings were hypercholesteremic. In answer to Dr. Aldersberg, we agree that this is not an uncommon disease. We are limited in Ann Arbor in the number of persons we can study by our laboratory facilities. We found families in the department of internal medicine, which is not an unusually large staff. In our experience, arcus juvenilis is much more diagnostic for essential familial hypercholesterema than arcus senilis. We feel that a better term is heterozygote abnormal, which Dr. Fliegelman used.

I do not feel that this is the proper place to discuss the therapy, which we will make the subject of a later paper and which we have been working on for about a year and a half. We agree with a number of Dr. Adlersberg's published reports, and we have not been quite in agreement with some others. I might add that we did from three to fifteen cholesterol tests for each subject.

EOSINOPHILIC GRANULOMA OF THE SKIN

Report of Three Cases

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EOSINOPHILIC granuloma of the skin is a new and not yet well defined disease entity. Occasional case reports under this diagnosis have appeared in the European literature since 1937. In the United States the disease received little attention until 1946. Since then, however, five papers on this subject have been published,[1] among them one from Boston.[1d] Nineteen cases in which the disease was diagnosed as eosinophilic granuloma of the skin are now recorded in the literature.

Three additional cases have recently been seen in Boston. The appearance in these cases, clinically as well as histologically, was almost identical with that in the first case reported from Boston.[1d] In fact, the clinical features of these 4 cases were so characteristic that in 1 instance (case 2) the diagnosis was made before biopsy.

REPORT OF CASES

CASE 1.—A 52 year old man first noticed in 1942 a small asymptomatic purplish lesion in the left preauricular region. The lesion slowly increased in size. In 1943 two similar lesions appeared: one in the left zygomatic and the other in the left infraorbital region. In 1946, a fourth lesion developed just below the infraorbital one.

On examination, in October 1946, the patient presented four sharply demarcated, purplish, slightly elevated plaques. The infiltrate in the plaques felt soft,

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From the Departments of Dermatology, Massachusetts General Hospital and Boston City Hospital.

1. (*a*) Buley, H. M.: Eosinophilic Granuloma of the Skin, J. Invest. Dermat. **7**:291, 1946. (*b*) Weidman, F. D.: The "Eosinophilic Granulomas" of the Skin, Arch. Dermat. & Syph. **55**:155 (Feb.) 1947. (*c*) Lewis, G. M., and Cormia, F. E.: Eosinophilic Granuloma: Theoretical and Practical Considerations Based on the Study of a Case, ibid. **55**:176 (Feb.) 1947. (*d*) Lever, W. F.: Eosinophilic Granuloma of the Skin: Its Relation to Erythema Elevatum Diutinum and Eosinophilic Granuloma of the Bone; Report of a Case, ibid. **55**:194 (Feb.) 1947. (*e*) Curtis, A. C., and Cawley, E. P.: Eosinophilic Granuloma of the Bone with Cutaneous Manifestations: Report of a Case, ibid. **55**:810 (June) 1947.

Fig. 1 (case 1).—Four sharply demarcated purplish, slightly elevated plaques are present.

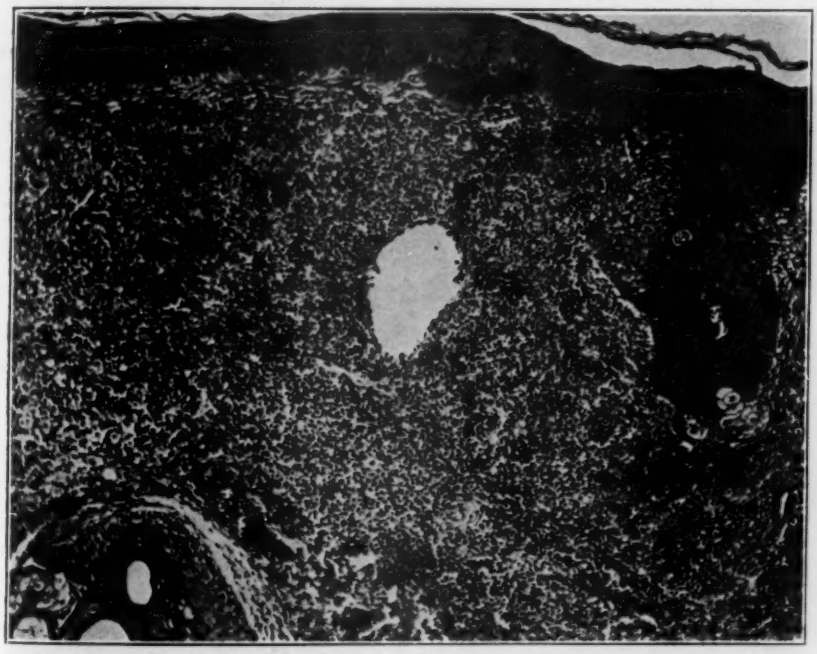

Fig. 2 (case 1).—Low magnification. The upper part of the corium is occupied by a diffuse infiltrate. A greatly dilated vessel is present in the center (× 100).

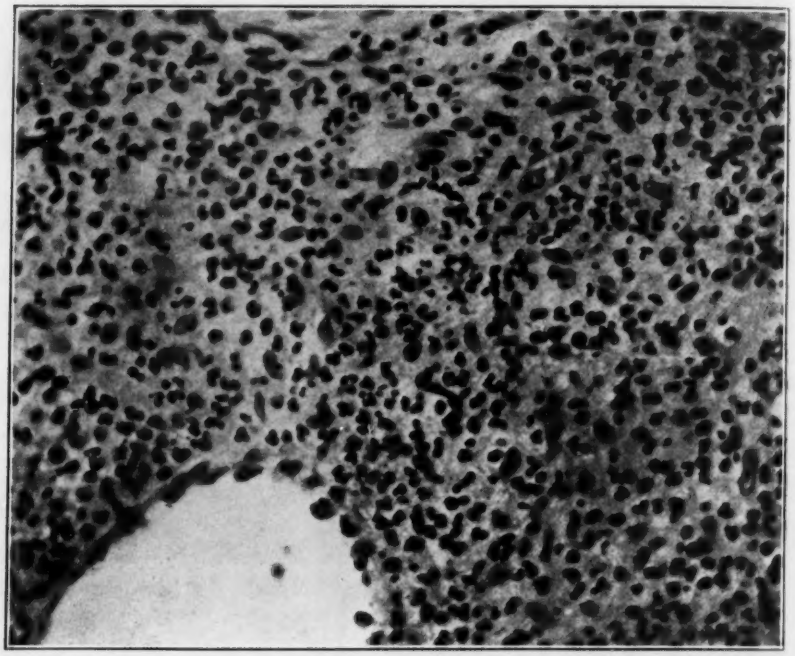

Fig. 3 (case 1).—High magnification. The infiltrate is composed largely of eosinophils and polymorphonuclear leukocytes. The remaining cells are almost all histocytes. The greatly dilated capillary shows swelling of its endothelium (× 400).

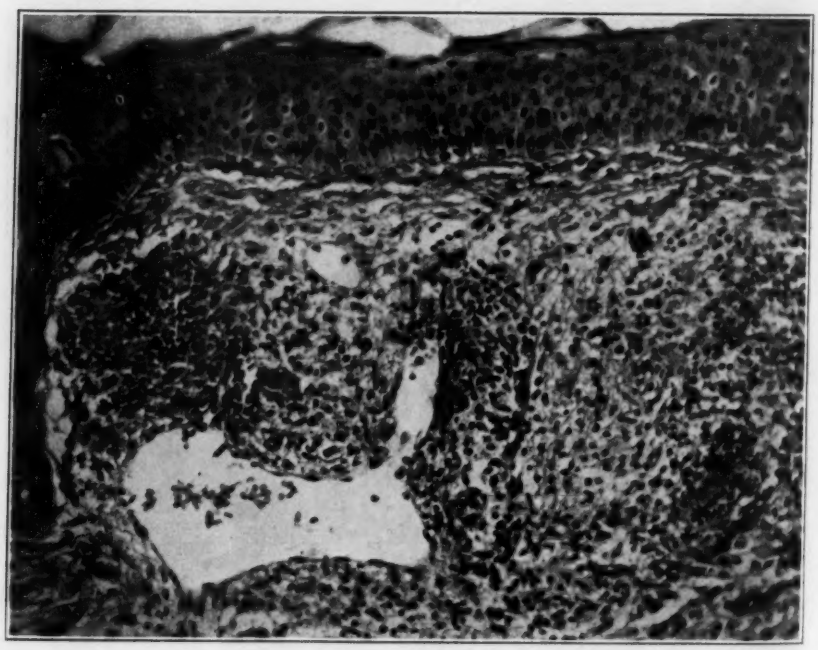

Fig. 4 (case 2).—An area taken from the border of the lesion shows the earliest stage. The infiltrate is not yet diffuse but is perivascular. The collagen is edematous. A greatly dilated capillary is shown. At the left upper pole of this capillary a focus of hemorrhage is present (× 200).

almost elastic to the touch. It was slightly irregular and felt nodular in parts. The lesions showed the following distribution (fig. 1): one in the left preauricular region, measuring 2.7 by 3.6 cm.; one in the left zygomatic region, measuring 2.9 by 3.1 cm.; one in the left infraorbital region, measuring 2.2 by 1.3 cm., and one just inferior to this last lesion, measuring 0.4 by 0.6 cm. General physical examination, as well as roentgenologic examination of the skull and long bones, revealed no abnormalities.

A biopsy revealed that the epidermis was of normal thickness, but the rete pegs were absent in most areas. Except for a narrow band of normal collagen directly beneath the epidermis, the upper half of the corium was occupied by a diffuse infiltrate (fig. 2). The infiltrate was densest around the capillaries. In the lower half of the corium, the infiltrate, instead of being diffuse, consisted of variously sized irregular patches. In a few areas it extended into the subcutaneous fat. The infiltrate was composed largely of eosinophils and polymorphonuclear leukocytes (fig. 3). In some areas these two types of cells constituted as much as 80 per cent of the infiltrate. The esosinophils were in part mononuclear and in part polymorphonuclear. The cytoplasm of the eosinophils only rarely showed distinct eosinophilic granules; usually it stained homogeneously eosinophilic. Frequently it was difficult to decide whether a given cell was an eosinophil or a neutrophil. The remaining cells of the infiltrate were almost all histiocytes. In only a few areas were a few lymphocytes and plasma cells noted. No areas of necrosis or abscess formation were seen. There were small foci of extravasated erythrocytes. Considerable amounts of hemosiderin were present throughout the infiltrate, but particularly in its upper portion. The hemosiderin was found extracellularly as well as within histiocytes. The capillaries were dilated, some of them considerably. They showed swelling of the endothelium. An occasional blood vessel showed fibrosis of its wall. The cutaneous appendages were normal; they were not invaded or destroyed by the infiltrate.

Staining for reticulum fibers (Foot stain) revealed a delicate densely meshed network of reticulum fibers throughout the infiltrate surrounding in some areas individual cells, but in most areas small groups of cells. An iron stain revealed that all the pigment present in the infiltrate was hemosiderin.

CASE 2.—A 40 year old man noted an asymptomatic purplish patch in the left preauricular region in April 1946. In January 1947 two small lesions appeared close to the original one. Examination on January 25 revealed a sharply demarcated, purplish red, slightly raised, soft irregularly infiltrated plaque in the left preauricular region, measuring 2 by 4 cm. in diameter, and two similar lesions, 0.3 cm. in size, close to the large lesion. A biopsy was done at that time. In August the large lesion had increased in size and had become confluent with the two satellite lesions. The entire area now measured 2.2 by 5 cm. The lesion was excised and the defect closed with a full thickness skin graft.

The biopsy specimen of January 25 was obtained from the periphery of the lesion. It showed essentially the same histologic appearance as that in case 1. There was a conspicuous amount of extravasated red blood cells. At the border of the lesion the infiltrate was not diffuse, but clearly perivascular. The collagen showed edema. Even at this earliest stage, the vessels showed dilatation, and foci of hemorrhages were present (fig. 4).

The specimen obtained at the time of complete excision showed a variable picture. At the margin the infiltrate was essentially the same as that observed

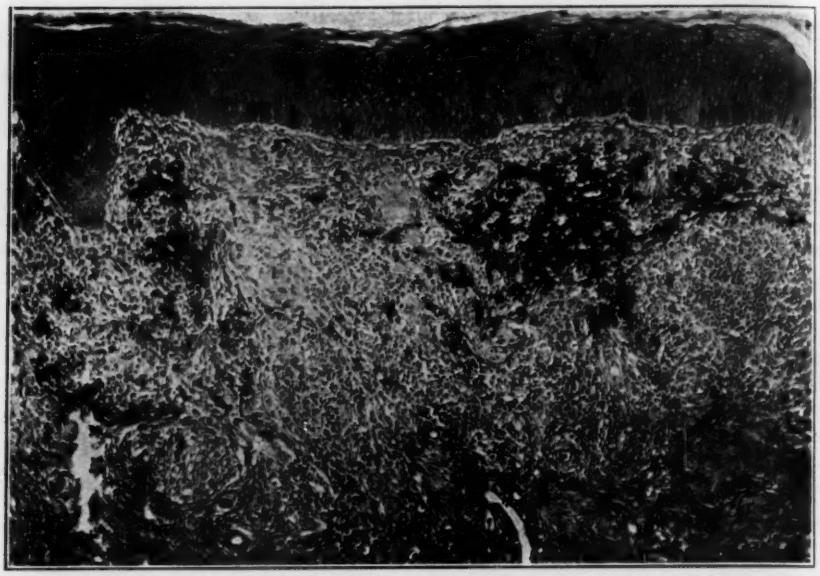

Fig. 5 (case 2).—Potassium ferrocyanide stain for iron. The infiltrate shows beginning fibrosis. Deposits of hemosiderin are present throughout the infiltrate, particularly in the upper part of the corium (× 100).

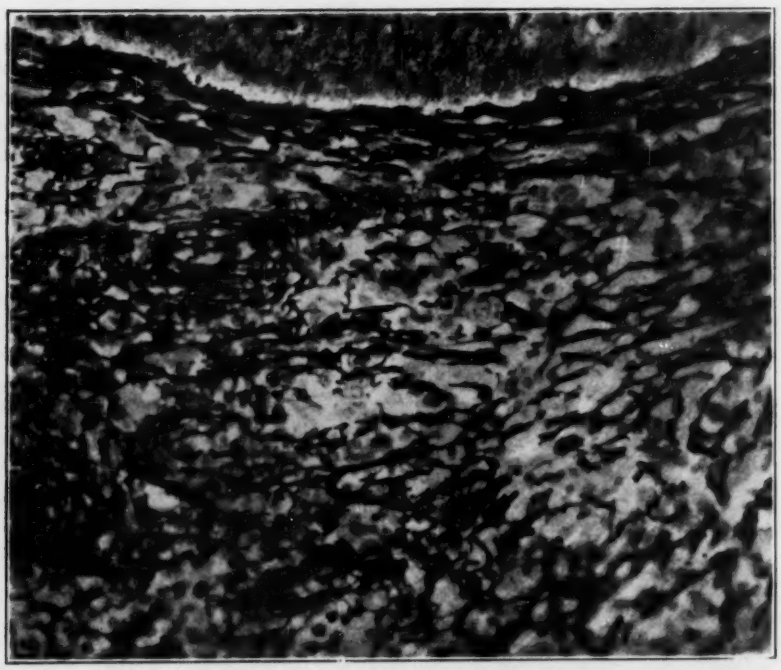

Fig. 6 (case 2).—Reticulum stain (Foot). On the left, where the infiltrate is composed predominantly of eosinophils and leukocytes, the reticulum network is finely meshed and the fibers themselves are delicate. On the right, where there is beginning fibrosis, the reticulum fibers are fewer and thicker (× 400).

in case 1. In the center the infiltrate was diffuse in some areas, while in others it was traversed by bands of collagen. The composition of the infiltrate varied. In areas of diffuse infiltration eosinophils and neutrophils were in the majority. In areas of beginning fibrosis, histiocytes, fibroblasts, lymphocytes and plasma cells were more numerous than eosinophils and neutrophils. The lymphocytes and plasma cells had a tendency to lie in focal collections. In areas of beginning fibrosis extravasation of erythrocytes was scarce or absent. The amount of hemosiderin, however, was considerable (fig. 5). The blood vessels located in areas of fibrosis showed fibrotic thickening of their walls.

Staining for reticulum fibers (Foot stain) showed a reticulum network of varying denseness (fig. 6). In areas in which eosinophils and neutrophils predominated, the reticulum network was finely meshed and the fibers themselves delicate. In areas undergoing fibrosis, the reticulum fibers were fewer and thicker. One could easily observe in many areas the transformation of reticulum fibers into collagen fibers.

Chemical analysis of the excised lesion revealed the values shown in table 1 (Dr. S. J. Thannhauser performed these tests).

CASE 3.—A 53 year old man was first seen on March 14, 1947, with the complaint of an asymtomatic slowly growing lesion in the right temple area, of six months' duration. The lesion measured 0.8 cm. in diameter, was reddish

TABLE 1.—*Results of Chemical Analysis of Lesion in Case 2*

	Sample with Lesion, Mg./100 Mg.	Sample Without Lesion, Mg./100 Mg.
Cholesterol (total)	0.230	0.342
(free)	0	0
Phospholipids (total)	1.490	1.280

purple, sharply demarcated, slightly elevated and soft and elastic to the touch. The lesion was excised. Examination on July 11 revealed that there was no recurrence at the site of excision. However, when on this date the patient was given a general examination, four lesions were noted on the back. The patient had not been aware of their presence. The largest lesion was located at the medial border of the left scapula and measured 1.1 by 0.7 cm. (fig. 7). Two lesions measuring 4 mm. each were present on the right shoulder, and one measuring 3 mm. was present over the left scapula. A biopsy of the largest lesion was performed.

The two excised lesions, one from the face and one from the back, showed essentially the same histologic picture. In a few areas, the infiltrate was diffuse and composed predominantly of eosinophils and polymorphonuclear neutrophils. In most areas, however, the infiltrate was divided into irregular patches by fibrotic collagen, and was composed predominantly of histiocytes, fibroblasts, lymphocytes and plasma cells, with only a few eosinophils and neutrophils. Small amounts of hemosiderin were present in the upper part of the corium. Fibrosis of the walls of vessels was a prominent feature (fig. 8).

COMMENT

The clinical and histologic appearance in the 19 cases of eosinophilic granuloma so far described in the literature is not uniform, except that the histologic picture in all cases is characterized by numerous

eosinophils and histiocytes. However, in the cases reported by Pasini [2] Wigley,[3] Buley [1a] and Lever [1d] and in the 3 presently reported there was such uniformity in the clinical and histologic appearance that the condition may well represent an entity apart from that in the other cases described under the diagnosis of eosinophilic granuloma of the skin. Taking Weidman's classification [1b] as a basis, they all represent the symptomatic type of eosinophilic granuloma of the skin. This type may be related to erythema elevatum diutinum.

On clinical examination, the lesions in the 7 patients consisted of sharply demarcated, slightly raised purplish plaques covered by a normal epidermis. They had a soft, almost elastic consistency. In the larger lesions a few nodular irregularities could be felt. The lesions were asymptomatic. They showed a tendency to increase slowly in size. Their number ranged from three to five. In 6 cases they were located

TABLE 2.—*Clinical Features in 7 Patients with Eosinophilic Granuloma of the Skin*

	Age of Patient	Sex	Duration (Yr.)	Number of Lesions	Location of Lesions	Size of Largest Lesion
Pasini [2]	69	F	8	4	Face	10.0 cm. (?)
Wigley [3]	46	F	2	4	Face	1.0 cm.
Buley [1a]	49	M	16	3	Face	0.8 cm.
Lever [1d]	47	F	11	3	Face	5.5 cm.
Case 1	52	M	4	4	Face	3.6 cm.
Case 2	40	M	1½	3	Face	5.0 cm.
Case 3	53	M	½	5	Face and back	1.1 cm.

exclusively on the face. In 1 case there were, in addition to one lesion on the face, four lesions on the upper part of the back (table 2).

On histologic examination an early (leukocytic) and a late (fibrotic) stage could be recognized. In several cases the two stages were present simultaneously. In Wigley's [3] and Buley's [1a] cases and in case 1, the lesions were those of the early stage. In Pasini's [2] case and case 2, beginning fibrosis was apparent. In Lever's [1d] case and case 3, there were, in addition to areas in the early stage, areas of pronounced fibrosis. Lesions in the early stage showed a diffuse infiltrate which was densest about the capillaries. It was composed of eosinophils, neutrophils and histiocytes. The eosinophils were predominantly polymorphonuclear, but some were mononuclear. The capillaries were decidedly dilated and showed swelling of the endothelial cells. In some cases there were areas of extravasation of red cells and deposits of hemosiderin (Lever's case [1d] and cases 1, 2 and 3). A dense net-

2. Pasini, A.: Granuloma eosinofilo (reticulo-endoteliosi proliferativa), Gior. ital. di dermat. e sif. **81**:1, 1940.

3. Wigley, J. E. M.: Sarcoid of Boeck; ? Eosinophilic Granuloma, Brit. J. Dermat. **57**:68, 1945.

work of fine reticulum fibers permeated the infiltrate. The cutaneous appendages were preserved. Lesions in the late stage showed greater polymorphism of cell types. The number of eosinophils and neutro-

Fig. 7 (case 3).—The largest of the four lesions on the back is shown.

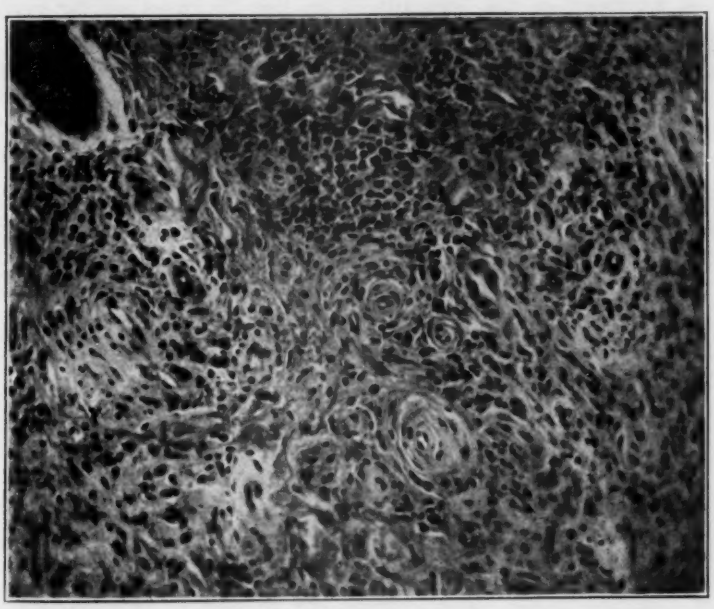

Fig. 8 (case 3).—The infiltrate shows a considerable degree of fibrosis. The infiltrate is composed predominantly of histiocytes, fibroblasts, lymphocytes and plasma cells. Only a few eosinophils and leukocytes are present. The vessels show thickening and fibrosis of their walls (× 200).

phils was greatly decreased, and lymphocytes, plasma cells and fibroblasts were present. The infiltrate, instead of being diffuse, was broken

up into irregular patches by thick strands of collagen. The walls of the vessels showed thickening and fibrosis of their walls. On staining for reticulum the transformation of reticulum fibers into collagen fibers could be observed in many areas. Foam cells and stainable lipids were found in only 1 of the 7 cases [1d]. Phagocytic activity was evident, however, in several other cases (cases 1, 2 and 3), inasmuch as hemosiderin was present within histiocytes.

It is not possible at the present time to decide whether or not eosinophilic granuloma of the skin is related to eosinophilic granuloma of the bone. So far, no unquestionable case with lesions of the bone as well as of the skin has been described. In Curtis and Cawley's case [1e] of eosinophilic granuloma of the bone with cutaneous manifestations, the lesions may have been those of Letterer-Siwe disease. In that disease, cutaneous as well as osseous lesions are known to occur.

Apparently eosinophilic granuloma of the skin is not a rare disease. It can, therefore, be expected that additional cases will soon accumulate, permitting a more exact appraisal of the nosologic position of this disease.

SUMMARY

Three cases of eosinophilic granuloma of the skin are added to the 19 cases recorded in the literature. In the 19 cases so far reported there was no uniform clinical and histologic appearance, except that histologic examination in all revealed numerous eosinophils and histiocytes.

However, in 4 of the reported cases and in the 3 presently reported there was such uniformity in clinical and histologic appearance that the disease in these cases may well represent an entity apart from that in the other cases.

ORAL IODINE THERAPY IN ACNE VULGARIS

Failure of Iodine, or the Equivalent of Iodized Salt, to Produce Pustular Exacerbations

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AND
G. B. UNDERWOOD, M.D.
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EARLY in 1945, various iron salts were being screened in patients with acne. The purpose was to study the effects of either the cation or the anions. An iron deficiency is common among adolescent girls. M. B. was a white married woman, aged 22, with pustular acne of six years' duration. In addition to routine therapy, she received ferrous iodide. An excellent clinical result attended the supplement. A sister, D. C., aged 19, presented a similar eruption, of four years' duration. Identical treatment was instituted with the exception that ferrous sulfide was prescribed. Her result was poor. Other patients with acne had received ferrous sulfide with indifferent effects. The subsequent course of the acne in these sisters made us consider that iodine may have influenced their response to treatment.

Cautiously iodine was prescribed for other patients. Two patients (cases 38 and 41) received an average of 56 mg. weekly (table). During twelve and ten weeks, respectively, of critical inspection, no exacerbations were noted. The improvement in their acne was ahead of schedule. The dosage in succeeding cases was then slightly increased. Weekly inspections failed to reveal any exacerbation. Thirty-four cases were observed over varying periods of time after iodine therapy was stopped. No late exacerbations were apparent. The amount of iodized salt required to supply an equivalent of iodine suggests that on a quantitative basis iodized salt does not unfavorably affect the course of acne vulgaris.

CLINICAL OBSERVATIONS ON IODINE SUPPLEMENT IN ACNE

A study of a possible iodine deficiency in acne has been under way over three years. Encouraging results have been obtained. The supplemental dosage has averaged about 280 mg. per week. The following clinical effects have been noted: 1. A flushing of the acne areas during the first month. This is especially apparent in patients with a sallow or yellowish complexion. 2. A gain in weight in the tall and slender persons. 3. The disappearance of comedos after three to six

Oral Iodine Dosage Compared with Intake from Iodized Salt *

Case No.	Patient	Age, Yr.	Sex	Iodine Compound	Weekly Iodine Dosage, Mg.	Weeks of Therapy	Total Iodine Intake, Gm.	Inspection During and After Iodine Therapy, Weeks	Iodized Salt Equivalent per Weeks of Therapy, Kg.†
1	J. A.	20	F	Strong iodine solution‡	0.336	14	4.7	19	62
2	S. A.	17	M	Strong iodine solution	0.168	9	1.51	9	20
3	H. A.	16	F	Strong iodine solution	0.112	19	2.12	19	28
4	M. B.	15	F	Strong iodine solution	0.560	8	4.48	8	59
5	A. B.	32	F	Strong iodine solution	0.168	15	2.52	15	33
6	D. B.	15	M	Potassium iodide	0.700	8	5.6	11	74
7	J. B.	14	M	Strong iodine solution	0.112	8	0.89	16	11
8	L. B.	19	F	Strong iodine solution	0.560	17	9.5	17	126
9	C. B.	18	M	Strong iodine solution	0.224	8	1.79	19	23
10	J. B.	14	F	Strong iodine solution	0.280	8	2.24	8	29
11	P. B.	15	F	Strong iodine solution	0.280	4	1.12	4	15
12	M. B.	17	F	Strong iodine solution	0.448	9	4.03	9	53
13	J. B.	17	F	Strong iodine solution	0.280	16	4.48	16	59
14	M. B.	22	F	Ferrous iodide	1.45	15	21.75	39	290
15	D. C.	19	F	Strong iodine solution	0.112	14	1.56	14	20
16	E. C.	13	F	Strong iodine solution	0.168	17	2.85	17	38
17	B. C.	23	F	Strong iodine solution	0.336	10	3.36	25	44
18	E. C.	21	M	Strong iodine solution	0.336	15	5.04	21	67
19	F. C.	22	F	Strong iodine solution	0.560	10	5.60	13	74
20	M. C.	19	F	Strong iodine solution	0.280	9	2.52	14	33
21	V. D.	17	F	Strong iodine solution	0.560	4	2.24	4	29
22	J. D.	21	M	Strong iodine solution	0.224	20	4.48	21	59
23	E. D.	14	M	Strong iodine solution	0.112	19	2.12	31	26
24	N. E.	22	F	Strong iodine solution	0.280	13	3.64	13	48
25	J. E.	14	F	Strong iodine solution	0.280	22	6.16	25	82
26	P. E.	18	F	Ferrous iodide	1.45	8	11.6	17	154
27	G. F.	15	M	Strong iodine solution	0.168	24	4.03	24	53
28	J. F.	21	F	Strong iodine solution	0.280	7	1.96	7	26
29	M. F.	17	F	Strong iodine solution	0.560	17	9.52	23	126
30	V. G.	17	F	Strong iodine solution	0.168	19	3.19	29	42
31	B. G.	18	F	Strong iodine solution	0.112	8	0.89	16	11
32	G. G.	21	M	Strong iodine solution	0.280	7	1.96	10	26
33	J. H.	13	M	Strong iodine solution	0.168	7	1.17	7	15
34	M. H.	17	F	Strong iodine solution	0.280	8	2.24	9	29
35	S. H.	18	M	Strong iodine solution	0.280	11	3.08	11	41
36	B. H.	21	F	Strong iodine solution	0.168	14	2.30	18	30
37	M. H.	18	F	Strong iodine solution	0.280	8	2.24	8	29
38	M. J.	20	F	Strong iodine solution	0.056	12	0.67	12	8
29	J. J.	16	F	Strong iodine solution	0.112	5	0.56	12	7
40	V. K.	14	F	Strong iodine solution	0.168	5	0.84	7	11
41	A. L.	18	F	Strong iodine solution	0.056	8	0.44	10	5
42	D. L.	23	F	Strong iodine solution	0.280	10	2.80	10	3
43	P. L.	13	F	Strong iodine solution	0.280	13	3.64	13	48
44	J. L.	13	M	Strong iodine solution	0.168	10	1.68	17	22
45	V. M.	23	F	Strong iodine solution	0.280	13	3.64	13	48
46	A. M.	17	F	Ferrous iodide	1.45	14	20.30	16	270
47	P. M.	17	F	Strong iodine solution	0.280	15	4.20	19	56
48	C. N.	29	F	Strong iodine solution	0.280	16	4.48	16	59
49	R. P.	16	M	Strong iodine solution	0.224	10	2.24	10	29

*Oral Iodine Dosage Compared with Intake from Iodized Salt *—Continued*

Case No.	Patient	Age, Yr.	Sex	Iodine Compound	Weekly Iodine Dosage, Mg.	Weeks of Therapy	Total Iodine Intake, Gm.	Inspection During and After Iodine Therapy, Weeks	Iodized Salt Equivalent per Weeks of Therapy, Kg.†
50	W. P.	15	M	Strong iodine solution	0.280	20	5.60	45	74
51	E. P.	20	F	Potassium iodide	0.700	10	7.00	12	93
52	G. R.	21	M	Strong iodine solution	0.056	8	0.448	18	5
53	J. R.	16	F	Strong iodine solution	0.280	9	2.52	9	33
54	A. R.	17	F	Strong iodine solution	0.224	20	4.48	25	59
55	E. R.	17	F	Strong iodine solution	0.168	8	1.32	8	17
56	E. S.	19	F	Strong iodine solution	0.280	6	1.68	6	22
57	E. S.	27	M	Strong iodine solution	0.112	7	0.78	7	10
58	O. S.	20	F	Strong iodine solution	0.168	5	0.84	5	11
59	C. S.	18	M	Strong iodine solution	0.280	7	1.96	7	26
60	J. S.	19	F	Strong iodine solution	0.280	10	2.80	14	37
61	M. S.	17	F	Strong iodine solution	0.280	13	3.64	13	48
62	I. S.	20	F	Strong iodine solution	0.280	9	2.52	9	33
63	S. S.	15	F	Strong iodine solution	0.168	7	1.17	7	75
64	O. S.	26	M	Strong iodine solution	0.224	12	2.68	15	35
65	M. U.	13	F	Strong iodine solution	0.168	4	0.67	4	8
66	R. W.	17	F	Potassium iodide	0.700	9	6.30	9	8
67	J. W.	15	M	Strong iodine solution	0.280	18	5.04	22	67
68	W. W.	20	M	Strong iodine solution	0.168	23	3.86	23	51
69	P. W.	16	M	Strong iodine solution	0.280	7	1.96	7	26
70	R. W.	19	F	Strong iodine solution	0.280	8	2.24	8	29
71	P. W.	17	F	Strong iodine solution	0.280	11	3.08	11	41
72	C. W.	20	F	Potassium iodide	0.700	12	8.4	40	112
73	H. W.	20	F	Strong iodine solution	0.280	8	2.52	9	33
74	F. W.	27	M	Strong iodine solution	0.280	11	3.08	11	41
75	R. W.	17	M	Strong iodine solution	0.280	10	2.80	10	38
76	M. W.	24	F	Potassium iodide	0.700	11	7.70	11	102
77	U. Y.	14	M	Strong iodine solution	0.280	16	4.48	21	59
78	N. C.	25	F	Strong iodine solution	0.280	16	4.48	16	59
79	L. B.	38	F	Strong iodine solution	0.224	4	0.89	4	11

* If the potassium iodide in iodized salt is not properly stabilized, the iodine content will rapidly migrate out of the product. The migration is favored by unusual conditions of temperature, humidity, sunlight, duration of storage and particularly the presence in the salt of inorganic salts of iron, copper and manganese. The use of iodized salt does not assure a uniform monthly intake of iodine. The iodine content may vary from the accepted level, 0.01 per cent to essentially 0. (From the Morton Salt Co. and Michigan and New York state departments of health.)

† Household salt is usually marketed in 26 ounce (454 Gm.) paper cartons.

‡ Lugol's solution.

weeks. 4. The lesions in colloid and cystic acne apparently undergoing liquefaction with the spontaneous drainage. 5. A clearing and brightening of the complexion. 6. A smoothening of the skin. 7. A favorable effect on the sequela, pits and scars.

REPORT OF A CASE

J. E., a white girl, aged 14, was seen early in May 1947 for severe acne of two years' duration. Comedos and pustules dotted the forehead, sides of the face, chin and neck. Lesions were present in all stages of evolution and involution. Deep pits showed the sites of healed lesions. The cheek prominences were occupied by a mass of hazelnut-sized purplish cysts.

The usual acne regimen was advised and roentgen therapy, 75 kilovolts, 5 milliamperes, 25 cm., 1 minute (80 r), each week. Twelve weeks of treatment produced no improvement. A consultation was obtained and the recommendations carried out. Four weeks of additional therapy had no effect. The cysts continued to deform the cheeks; comedos kept appearing and resolving as pustules. On September 12, iodine therapy was started, 5 drops daily of strong iodine solution. A week later, this was reduced to 3 drops daily. By October 10, all the active lesions had involuted. The iodine supplement was continued until December. She was discharged at this time with an excellent result.

DEVELOPMENTAL, ENVIRONMENTAL AND BIOCHEMICAL EVIDENCE OF A POSSIBLE IODINE DEFICIENCY IN ACNE

Four phases of growth are distinguished from birth to adulthood. The first phase of growth is rapid. It decelerates about the end of the second year. From the second to the tenth or eleventh year, the growth is about uniform, a weight gain of 2 to 2.8 Kg. per year. The third phase is characterized by a "spurt" in weight and height, associated with sexual maturity and puberty.[1] Acne eruptions usually appear during or after this rapid phase of development. If iodine requirements are minimal or subminimal during the prepuberty years, sudden growth would tend to produce a severe deficiency. The dietary histories of patients with acne have commonly revealed that the bulk of their calories came from food low or deficient in iodine. As the growth curve flattens out, an iodine deficiency would gradually be overcome. After varying periods following puberty, acne lesions tend to disappear.

During the fall of 1947 over 500 male high school freshmen and sophomores were given the "line type" dermatologic examination. These boys were going through or had just completed their most rapid development. To observe the acne areas free from comedos or pustules was rare. The examinations were made toward the close of two months of extremely hot and humid weather. The sweat glands are accessory organs for the loss of iodine from the body. An important nutritional question with reference to iodine metabolism is the effect of a hot environment on the losses of iodine from the body and on iodine requirements, particularly as this effect may involve the activity of the

1. Nelson, W. E.: Mitchell-Nelson Textbook of Pediatrics, ed. 4, Philadelphia, W. B. Saunders Company, 1945.

sweat glands.[2] Of interest in this respect are the reports [3] on tropical acne.

About 10 per cent of the body iodine is present in the skin. Increased excretion of iodine in the urine has been observed during menstruation, pregnancy, acute infections and during periods of excitement.[4] The thyroid is apparently the site for the conversion of dietary carotene into vitamin A.[5] Iodine is an essential component of the thyroid hormone. If a dietary lack of iodine affects the ability of the thyroid to form vitamin A, it is possible that a cutaneous deficiency of this vitamin may be in part an iodine deficiency. The observation of keratotic plugging of the sweat ducts in prickly heat [6] may be proved to reflect a deficiency of one or both of the components necessary for the thyroid to elaborate vitamin A. Future investigations may well revise upward the dietary requirements of iodine.

CONCLUSION

The total iodine intake and the weeks of observations during and after iodine therapy suggest that, on the basis of the cases herein discussed, iodized salt does not unfavorably affect the course of acne vulgaris.

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2. Spector, H.; Mitchell, H. H., and Hamilton, F. S.: The Effect of Environmental Temperature and Potassium Iodide Supplementation on the Excretion of Iodine by Normal Human Subjects, J. Biol. Chem. **161**:137, 1945.

3. Novy, F. G., Jr.: Tropical Acne, California Med. **65**:274, 1946. Allington, H. V.: Acne Vulgaris Occurring in the Tropics in a Pigmentary and Pilosebaceous Nevus, Arch. Dermat. & Syph. **52**:322 (Nov.-Dec.) 1945. Sulzberger, M. B.: Tropical Acne, in Year Book of Dermatology and Syphilology, 1944-1945, Chicago, The Year Book Publishers, Inc., 1946, p. 281.

4. Cantarow, A., and Trumper, M.: Clinical Biochemistry, ed. 3, Philadelphia, W. B. Saunders Company, 1945, p. 215.

5. The Thyroid and Vitamin A, editorial, J. A. M. A. **137**:91 (May 1) 1948.

6. Sulzberger, M. B., and Zimmerman, H. M.: Studies on Prickly Heat, J. Invest. Dermat. **7**:61, 1946.

GUMMA OF THE LUNG

Report of a Case

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GUMMA of the lung is conceded by most writers on the subject to be a rarity, especially as a manifestation of acquired syphilis. The diagnosis of gumma of the pulmonary parenchymal tissue in all cases heretofore reported has been either clinical or established at necropsy. The case to be reported is unique in that the disease was suspected clinically and confirmed histologically in a living patient by examination of lung tissue removed by lobectomy.

It is not within the scope of this report to review the literature, as little has been added since the presentation of Carrera [1] in 1920.

The diagnosis of gumma of the lung rests on several criteria, which may be divided into four broad categories: clinical, radiologic, therapeutic and pathologic.

Clinically, there is little to distinguish gumma of the lung from a host of other localized chronic pulmonary lesions, particularly tuberculosis, deep mycoses of the actinomyces and nocardia groups, discrete areas of pneumonitis of bacterial origin, neoplasms, localized bronchiectasis and pulmonary abscess. The criteria outlined by Pearson and De Navasquez,[2] as quoted by Kulchar and Windholz,[3] seem adequate:

1. An anomalous history of pulmonary disease, often with hemoptysis, productive cough, loss of weight, and fever, either of brief duration or extending over a period of years.
2. Exclusion of the commoner causes of pulmonary symptoms such as pneumonia, neoplasm, fungous infections, and tuberculosis, the latter by repeated failure to find tubercle bacilli in the sputum.
3. The presence of a history of syphilitic infection or associated syphilitic lesions in other organs and of a positive serologic test for syphilis.
4. The effect of antisyphilitic treatment on the lesion.
5. X-ray appearance, particularly in association with the response to treatment.

From the Department of Dermatology, College of Physicians and Surgeons, Columbia University and the Vanderbilt Clinic, New York.

1. Carrera, J. L.: A Pathologic Study of the Lungs in One Hundred and Fifty-Two Autopsy Cases of Syphilis, Am. J. Syph. **4**:1, 1920.
2. Pearson, R., and De Navasquez, S.: Syphilis of the Lung, Guy's Hosp. Rep. **88**:1, 1938.
3. Kulchar, G. V., and Windholz, F.: The Clinical, Radiologic and Pathologic Aspects of Late Pulmonary Syphilis: Effects of Penicillin Therapy, Am. J. Syph., Gonor. & Ven. Dis. **31**:166, 1947.

As these criteria were postulated in 1938, prior to the era of penicillin therapy, some additions and revisions are in order. The drugs then in use, the arsenicals and heavy metals, could be considered relatively specific for lesions of syphilis, and the therapeutic test was a not absolute, but a highly suggestive, point in differential diagnosis. With the wide spectral range of penicillin among micro-organisms, a therapeutic test with this antibiotic can no longer be regarded as valid, especially in attempts to rule out pulmonary diseases in the nontuberculous bacterial group. It is well to remember, too, that a history of syphilis is often lacking and that tertiary lesions of syphilis have been known to occur in the absence of a positive serologic reaction. Another stumbling block frequently encountered is a false positive serologic reaction in the presence of pulmonary lesions of other than syphilitic origin. However, these are usually of low titer and of transient nature. Lesions of specific bacterial or mycotic origin can usually be ruled out by the isolation of the organism, either by direct examination or by cultural methods, and neoplastic lesions by their progression and lack of response to any type of therapy other than operation or irradiation.

It soon becomes obvious that the pitfalls to the absolute diagnosis of gumma of the lung are so numerous that only histologic examination of the diseased tissue will suffice. This conclusion is in agreement with that of Carrera after his exhaustive study of the subject. The diagnosis would be even more firmly established if Treponema pallidum could be found in the diseased tissue, in conjunction with the classic tissue reaction to syphilis. Only three investigators have found T. pallidum in the pulmonary lesions of acquired syphilis (Koch, Schmorl and Warthin). It is generally conceded, however, that this is not a *sine qua non*, provided that the tissue reaction is compatible with syphilis and that other diseases can be ruled out. In my case I did not find, nor did I expect to find, T. pallidum in the pathologic tissue, because large doses of penicillin had been administered prior to the removal of the gummatous lobe. Nevertheless, a careful but fruitless search for the organism was conducted by employment of the Levaditi staining technic. Acid-fast bacilli likewise could not be found.

REPORT OF A CASE

J. W., a 39 year old American Negro, applied for care at the Presbyterian Hospital on Oct. 27, 1947, with a chief complaint of "cough and cold in the left side of the chest" of thirty-seven days' duration. The patient stated that he had been well until September 20, when he had a slight chill, followed by the pain in the left side of the chest. The pain was dull and accentuated by his lying on his left side. Cough was productive of a small quanty of greenish yellow sputum. No rust-colored or bloody sputum was raised. He was seen by a local physician who had a pulmonary roentgenogram made, which the patient said showed a lesion

in the lower lobe of the left lung. He was given cough syrup, which relieved the cough slightly, but this recurred when the oral medication was discontinued. The pain also recurred, without change in intensity or location. There were no further chills, and he had never noticed night sweats. Since the onset of his illness, the patient had noticed moderate fatigue and dyspnea on exertion, and he had lost about 10 pounds (4.5 Kg.) in weight.

There was no history of either primary or secondary lesions of syphilis. In 1927 the patient received two or three intravenous injections "for his blood." In 1945 a private physician gave him three injections in the hip, of an intended course of six, of "yellow medicine."

The patient had had a cystotomy in 1927 for "bladder stones," and at the same time the left testicle and the glans penis were removed. No further information about these measures could be obtained. Otherwise the past history was not

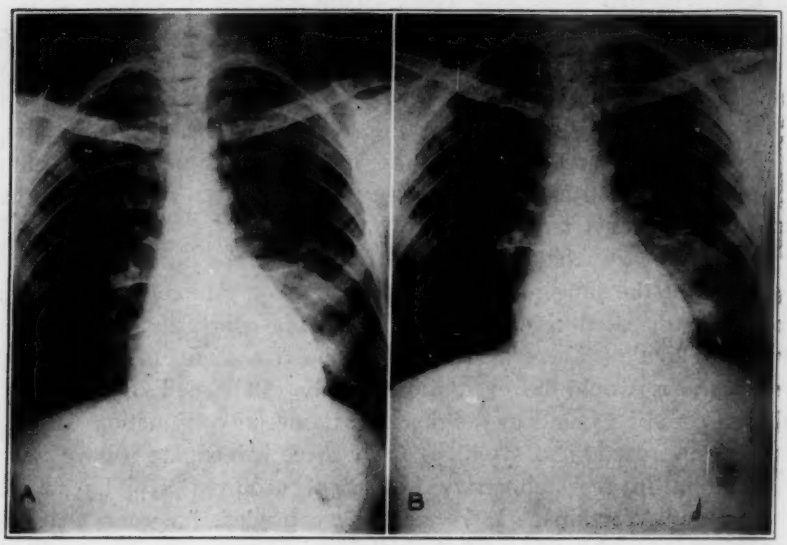

Fig. 1.—*A*, Roentgenogram of the chest, taken Oct. 27, 1947, showing a localized inflammatory lesion in the lower lobe of the left lung. *B*, roentgenogram of November 26. After a month of penicillin therapy, the lesion shows only slight diminution in size.

remarkable, and the family history was noncontributory. No one in his immediate family had suffered from tuberculosis, to his knowledge.

On admission the patient's temperature was 98.4 F., pulse rate 75, respiration 18 and blood pressure 115 systolic and 80 diastolic. His general appearance was that of a well developed moderately emaciated Negro, who did not appear acutely ill. The pupils were round and equal and reacted to light and accommodation. There were no significant abnormalities of the nose, throat, neck or head. Examination of the heart revealed an organ of normal size without murmurs, thrills, arrhythmia or other remarkable signs. On percussion of the chest an area of dulness was noted over the lower lobe of the left lung posteriorly. Auscultation revealed tubular breathing with crepitant rales on inspiration over an area 5 cm. in diameter below the inferior angle of the left scapula. On examination of the abdomen a scar in the suprapubic area was noted, but there were no other

abnormalities in this region. The glans penis and left testicle were absent. A stricture was noted on digital examination of the rectum. The prostate was normal in size and consistency. Deep and superficial reflexes were regarded as normal, as was appreciation of pain, temperature, touch, pressure and proprioception.

On the day of admission the hemoglobin was 13.4 Gm. (Sahli), erythrocytes 4,400,000 and white blood cells 12,650, with a differential count of 62 polymorphonuclear leukocytes, 36 lymphocytes and 2 eosinophils. The erythrocytes revealed

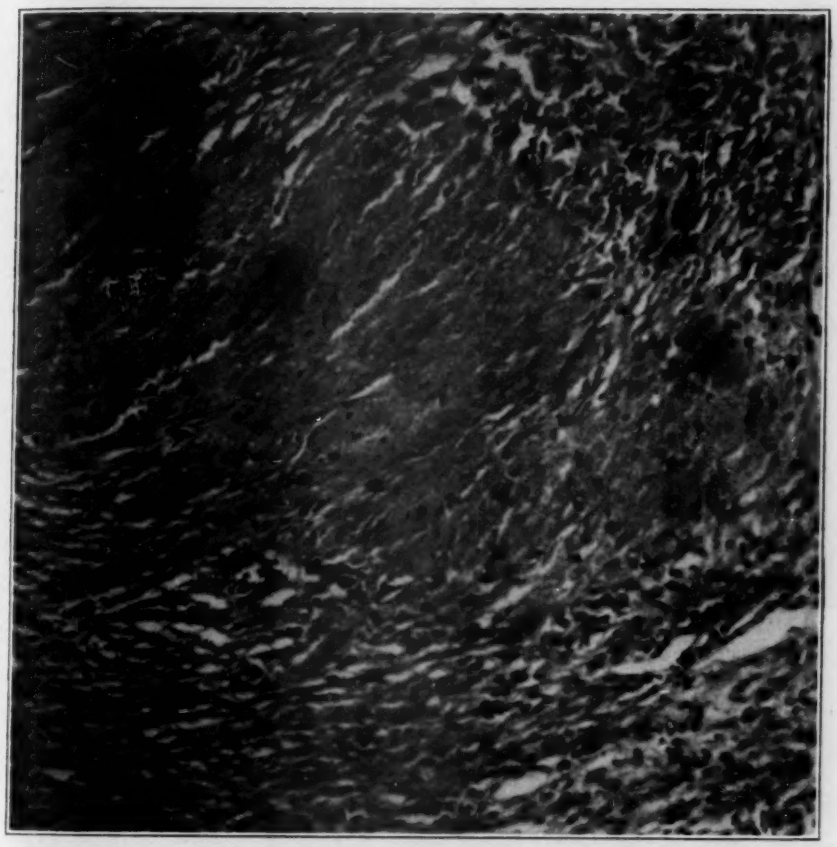

Fig. 2.—Low power photomicrograph showing caseation necrosis, and peripheral infiltration of plasma cells and lymphocytes.

no anisocytosis or poikilocytosis; no malarial parasites were seen, and platelets were present in normal numbers. Succeeding hemograms were essentially the same.

Examination of the sputum revealed no acid-fast bacilli. Results of tests for cold agglutinins were negative.

A roentgenogram of the chest on October 27 (fig. 1 *A*) showed a large well defined lobulated shadow of increased density located posteriorly and medially in the left hemithorax. No abscess cavity was visualized.

On October 28 the erythrocyte sedimentation rate was 134 mm. in sixty minutes.

Reexamination of the sputum on October 29 still revealed no acid-fast bacilli. A stool examination on the same date showed no ova or parasites. A thoracentesis was performed, but no fluid could be obtained. Serologic tests for syphilis on October 28 and October 30 gave strongly positive Kline and Wassermann reactions in both instances.

Acid-fast stains on October 31 again failed to reveal tubercle bacilli. Penicillin therapy was begun on this date, 400,000 units being given daily until November 12, when the dosage was increased to 1,000,000 units daily and continued through

Fig. 3.—Low power photomicrograph of pulmonary tissue showing obliterative changes in small blood vessels and a sparse round cell infiltration. These elements have largely replaced the alveolar structure (hematoxylin and eosin).

November 27. The total quantity administered was 20,800,000 units. During this period, 200 mg. of bismuth compound was given weekly and 45 drops of potassium iodide by mouth daily.

On November 3 lumbar puncture was performed and clear fluid obtained. Examination of this fluid showed 1 lymphocyte and 27 mg. of protein. The Wassermann reaction and colloidal gold curves were negative.

Examination of the serum protein on November 5 showed a total of 9.1 Gm. per hundred cubic centimeters, with albumin 4.3 Gm. and globulin 4.8 Gm. per hundred cubic centimeters.

Reexamination of the pulmonary lesion by roentgenogram on November 5 showed no appreciable change. Bronchoscopic examination on November 11 disclosed no abnormalities. Results of tuberculin tests were positive to a dilution of 1 : 100 and negative to 1 : 10,000.

By November 12 the patient was subjectively improved, although only slight improvement could be noted in the roentgenograms of the chest. The possibility of pulmonary neoplasm seemed real at this time, and a lobectomy was scheduled for December 2. Several roentgenograms during the intervening time still showed little change in the lesion (fig. 1 *B*). A lobectomy, of the lower lobe of the left

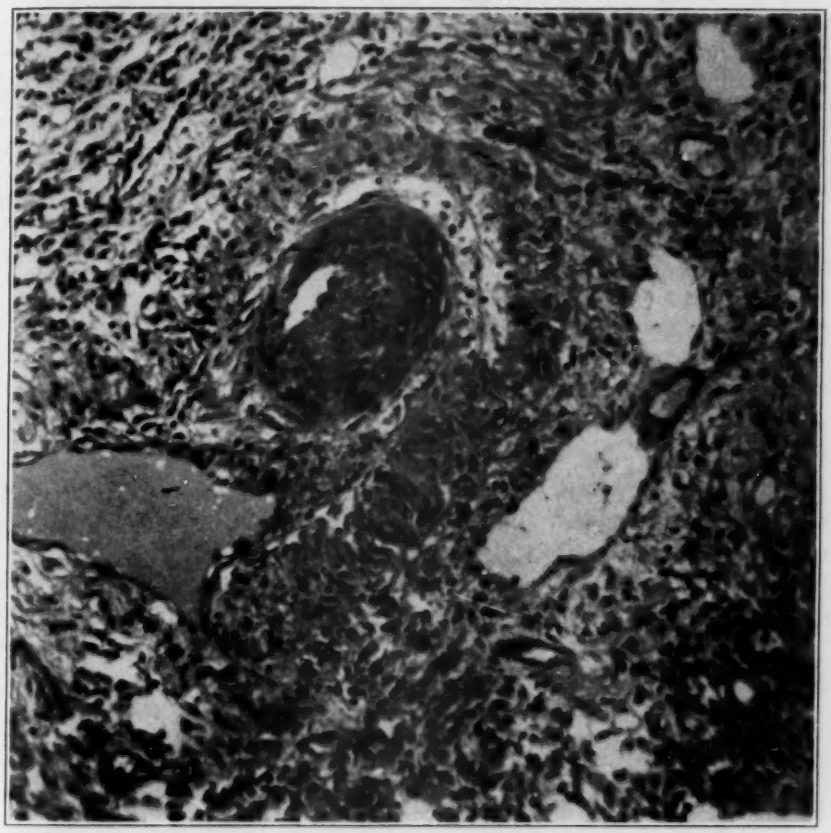

Fig. 4.—Low power photomicrograph of pulmonary tissue showing an organized thrombus in a medium-sized vessel and a diffuse round cell infiltrate.

lung, was performed on December 2, and the patient recovered uneventfully, being discharged from the hospital on December 12, to be followed in the outpatient department.

On three occasions since the patient's discharge from the hospital, serologic tests for syphilis were made, the last on June 3, 1948, and the Kline and Wassermann reactions of all specimens were strongly positive.

Gross pathologic examination of the tissue removed at operation revealed a firm irregular oval mass occupying the major portion of the lower lobe of the left

lung. The visceral pleura was smooth and glistening, except for an area 7 by 5 cm. overlying the mass, where it was thickened, firm and light gray. The cut surface revealed a wedge-shaped nodular mass 7 by 7 by 4 cm., situated at the periphery of the lung. The mass was composed of firm gray well circumscribed nodules which extended to the pleura.

Microscopic examination disclosed a multilocular lesion composed of necrotic fibrous tissue and lung parenchyma. The normal lung architecture had been destroyed by enormous amounts of fibrous tissue which had in turn become necrotic (fig. 2). The necrosis, however, for the most part, was of that type which leaves faint cellular and structural images. It did not show the complete caseation necrosis typical of tuberculosis; nevertheless, there were a few areas where the necrosis was complete. The fibrous tissue was cellular and not too dense in its arrangement. An occasional multinucleated giant cell was seen.

The remainder of the lung parenchyma also showed a disorganized arrangement of the alveoli due to widespread fibrosis. The alveoli, when distinguishable, had swollen endothelial cells, giving the appearance of cuboidal epithelium. Many alveoli had accumulations of large foamy macrophages. In addition, there was a good deal of focal round cell infiltration, consisting mostly of plasma cells. Some of these collections were around the blood vessels (figs. 3 and 4), but it was not a constant feature. Certain blood vessels showed endothelial proliferation, while at the periphery of the lesion new vessels could be seen in great abundance. A Levaditi stain failed to reveal the unequivocal presence of spirochetes. The pathologic diagnosis was compatible with gumma of the lung.

SUMMARY

A case of gumma of the lung is presented, with histologic confirmation. The diagnosis was made in a living patient, from tissue removed by lobectomy. To my knowledge, such a case has not heretofore been reported. The clinical, roentgenologic and pathologic observations are described in detail.

A NEW BODY DEODORANT

Its Nonallergenic Properties and Usefulness

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UNTIL recently foul odors in hospitals and patients' sickrooms had to be tolerated because no practical means of preventing or eliminating them was known. However, because of the physiologic and psychologic effects of unpleasant odors on patients, hospital personnel and visitors, constant search for a good method of deodorization was being made.

At the time this report was being written, the most practical method of deodorization and the only one to be accepted for promotion through American Medical Association publications was a specially prepared deodorant solution of 1.2 per cent potassium mercuric iodide, 2.5 per cent sodium hydroxide and potassium iodide, 0.24 per cent in distilled water.[1] As originally introduced for hospital and sickroom deodorization, the solution was used in two ways: 1. If the odor had already escaped into the room, the solution was poured into a specially designed unit which sucked the odor-laden air into the machine, blew it against the solution and then the deodorized air was blown back into the room. None of the solution or any of its active ingredients escaped into the air. Another distinct advantage was the decided reduction in the number of bacteria in the air passing over the solution in the unit.[2] 2. When odors emanate from suppurative surface lesions, burns, osteomyelitis, colostomy openings and the like, they may be effectively combated at their source by placement of a few layers of gauze soaked in the solution over the surgical dressing or colostomy opening. When the odor comes in contact with the moistened gauze it is destroyed and hence cannot contaminate the air.[3] Both of these methods are satisfactory and convenient. However, it was not possible to use either of these methods to take care of odors originating in axillary folds, regions of the pubis and mammae. In cases of this kind, the deodorant must be applied directly to the cutaneous surface. Deodorizing agents applied to the

Dr. H. O. Lloyd, Jefferson City, Mo., assisted in the study.

1. Marketed under the name of aero-klenz.®

2. Danforth, T. F.; Rudig, D. M., and Fishbein, W. I.: Machine and Solution to Control Air Borne Bacteria, Mod. Hosp. (no. 5) **66**:100 (May) 1946.

3. Schnedorf, J. C.: An Experimental Investigation of a Deodorant, personal communication to the author.

skin must not only be effective but bland, nonirritating and nonsensitizing. Previous search and clinical studies have established the bland and nonirritant properties of this deodorant solution.[4] The purpose of this investigation was to determine whether the deodorizing solution had any sensitizing properties and at the same time study its effectiveness as a deodorant for personal use. The deodorant solution used in this study (hereafter referred to as deodorant or test solution) consisted of 0.12 per cent potassium mercuric iodide, 0.25 per cent sodium hydroxide and 0.02 per cent potassium iodide in distilled water.

PROCEDURE

This study was carried out on a group of volunteers who were prisoners at the Missouri State Penitentiary, Jefferson City, Mo. One of the prison physicians cooperated in this study. With this cooperation it was possible for the subjects to be kept under almost constant observation. The plan of study was as follows:

On all subjects patch tests were made with the deodorizing solution to be studied before the solution was applied to the body in any other manner. Patch tests remained on patients for forty-eight hours unless otherwise indicated, and at the end of that period the results were observed. Any subject who showed a positive reaction at this time was excluded from further study. Subjects showing any evidence of dermatitis, particularly in the axillary region, which might later be confused with contact dermatitis arising from the application of the solution being tested, were not included in the study. All remaining subjects were instructed to apply the test solution to the axilla twice a day for a period of thirty days, unless otherwise instructed. The subjects were told to report any redness, eruption or increased sensitivity, and when these signs or symptoms developed, to stop the application of the solution. After more than thirty days of application, the subjects discontinued the use of the solution, but after a rest period of approximately one week the subjects were instructed again to apply the same solution to the axillas, this time for three days. At the end of three days the subjects were again examined for the presence of any eruption which might be contact dermatitis or any other dermatitis that might be due to the drugs in the solution. At the same time, all of these subjects were again given patch tests with the original solution. This group included those that had or did not have eruptions at this time and included also those in whom eruption developed before the thirty day period was completed. All in this group who showed positive

4. Isenberger, R. M.: Investigation of Deodorant Solution, personal communication to the author.

or doubtful reactions to patch tests were, after a lapse of time, given patch tests with six different items. These six patch tests were as follows:

One patch test was made with a 0.12 per cent of potassium mercuric iodide solution; one, with a 0.25 per cent sodium hydroxide solution; one, with a 0.02 per cent potassium iodide solution. One was made with cloth previously used in the patch test to contain the solution being tested. One was made with the adhesive and cellophane patch test material (elastopatch,® Duke Laboratories). The remaining patch test was made with the original test solution, containing all the ingredients.

RESULTS

During the study all patch tests that resulted in a doubtful reaction were repeated. It is known that many subjects applied the solution to the axillas in excess of the number of times requested.

*Reaction to Patch Tests (645 Patients)**

Test Material	Positive Reactions
Potassium mercuric iodide solution (0.12 per cent)	1
Sodium hydroxide solution (0.25 per cent)	3
Potassium iodide solution (0.02 per cent)	1
Cloth used with solutions	0
Adhesive and cellophane †	0
Test solution with all ingredients	7

* One subject showed a positive reaction to the test solution, solution of sodium hydroxide and also potassium mercuric iodide.
† Slightly positive reactions to adhesive tape were not recorded. No reactions here were positive enough to be confused with positive reactions to other test materials.

Three subjects, during the study, presented an axillary eruption thought to be contact dermatitis. Only 1 of these 3 showed a positive reaction to a patch test. This subject showed a positive reaction to the test solution and to sodium hydroxide solution. Two subjects showed an acneform eruption scattered over the trunk and arms but had negative reactions to all patch tests. Two subjects gave a history of a generalized eruption after two weeks of application of the test solution. The history suggested urticaria. The reactions in these cases were negative to all patch tests. The presence of atopy or other allergies in the subject or in his family evidently had no relationship to the allergic reaction to the test solution studied. At any rate, most of the subjects with histories of allergies or a family history of allergy showed no evidence of an allergic reaction to the test solution.

DEODORIZING PROPERTIES

All subjects were questioned individually regarding the efficacy of the solution in destroying the odors from the perspiration of the axilla.

Questioning was done at the end of the thirty day period during which time the subjects applied the solution twice a day. Results were as follows:

Total number of subjects	645
Number who stated that the odor was stopped	512
Number who stated that no change was noted	34
Number who stated that the odor was decidedly decreased	82
Number indifferent to presence or absence of odor	17

It must be remembered that the test solution was usually applied not more than twice daily. It is entirely logical that the prisoners, during excessive work, lost much of the solution from their body during the interim between applications. Also, it must be taken into consideration that not all prisoners were honest in their application. These facts must be taken into consideration before evaluation of the deodorizing effect. Many subjects during this study evidently used the test solution much more than twice a day, since many repeatedly called for refills of their bottles, making particular mention of the fact that they wanted the solution to kill perspiration odor. At the beginning of the study subjects were not told that the solution would cancel odors, but were asked to note whether the solution deodorized, stopped or made odors worse.

CONCLUSIONS

1. The product tested, containing 0.12 per cent potassium mercuric iodide, 0.25 per cent sodium hydroxide and 0.02 per cent potassium iodide, is, according to this study, relatively nonsensitizing when applied to the human body. The mercurial ingredient of the solution is evidently nonsensitizing as compared with other mercurial preparations.

2. This solution may be applied to the skin over long periods of time with little danger of the development of allergic reactions.

3. This solution, in my opinion, has a definite deodorizing quality and could well be the answer to a physician's need for a deodorizing medicament.

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